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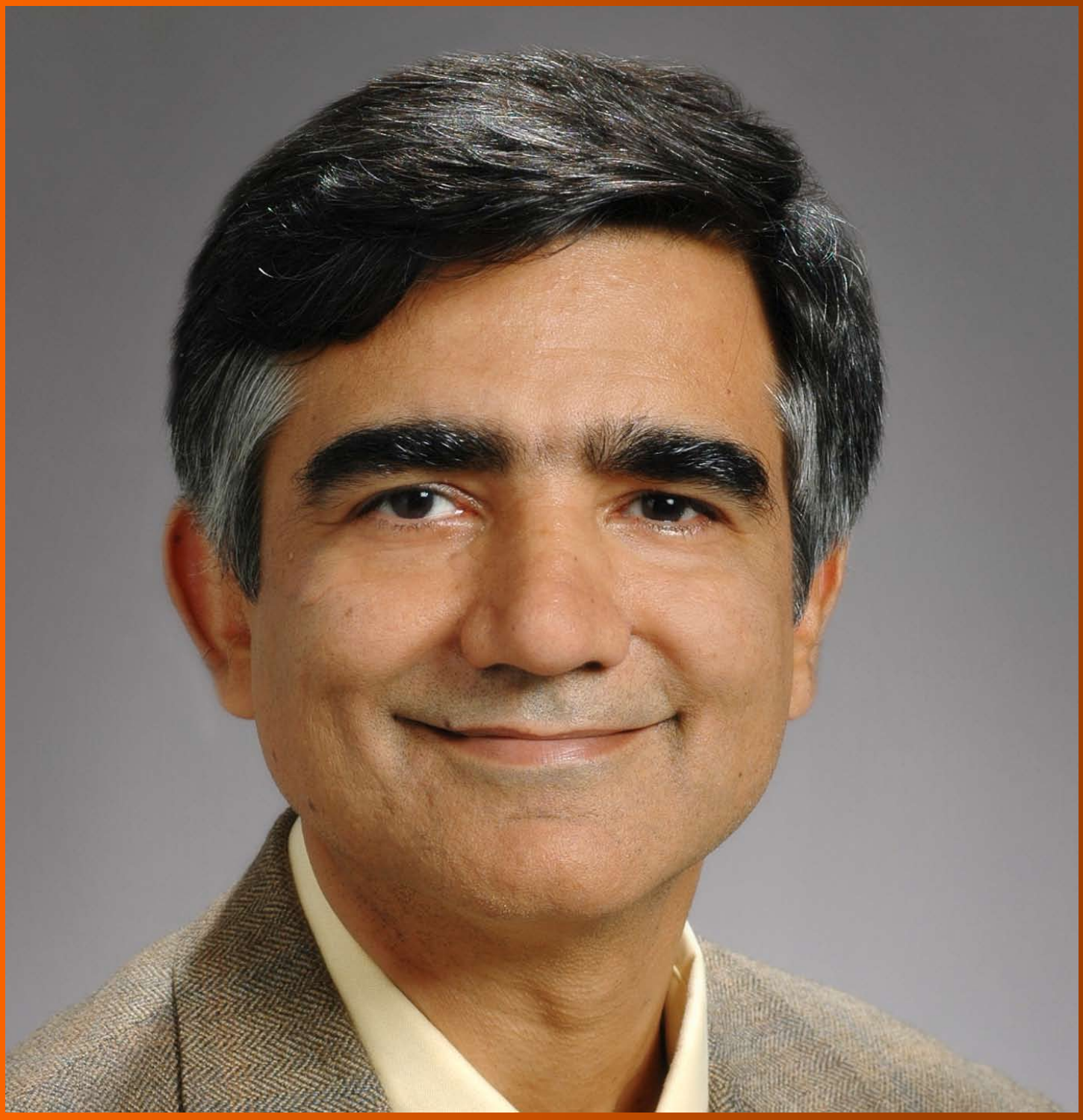

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REVIEW

Entrapment neuropathies in diabetes mellitus

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Abstract

Neuropathy is a common complication of diabetes mellitus (DM) with a wide clinical spectrum that encompasses generalized to focal and multifocal forms. Entrapment neuropathies (EN), which are focal forms, are so frequent at any stage of the diabetic disease, that they may be considered a neurophysiological hallmark of peripheral nerve involvement in DM. Indeed, EN may be the earliest neurophysiological abnormalities in DM, particularly in the upper limbs, even in the absence of a generalized polyneuropathy, or it may be superimposed on a generalized diabetic neuropathy. This remarkable frequency of EN in diabetes is underlain by a peculiar pathophysiological background. Due to the metabolic alterations consequent to abnormal glucose metabolism, the peripheral nerves show both functional impairment and structural changes, even in the preclinical stage, making them more prone to entrapment in anatomically constrained channels. This review discusses the most common and relevant EN encountered in diabetic patient in their epidemiological, pathophysiological and diagnostic features.

Key words: Diabetes mellitus; Neuropathy; Diabetic neuropathy; Median entrapment neuropathy at the wrist; Ulnar entrapment neuropathy at the elbow; Ulnar entrapment neuropathy at the wrist; Carpal tunnel syndrome; Electrodiagnosis; Tarsal tunnel syndrome

Core tip: Diabetic neuropathy syndromes include both generalized and focal/multifocal forms. Entrapment neuropathies (EN) are remarkably frequent in the focal forms and may be the earliest neurophysiological abnormalities in diabetes, even in the absence of a generalized polyneuropathy. Based on a pathophysiological hypothesis, diabetic patients' peripheral nerves, damaged by the altered glucose metabolism, show both functional impairment and structural changes. This makes them more susceptible to chronic compression in anatomically constrained channels. Therefore, EN may be considered a neurophysiological hallmark of peripheral nerve involvement in diabetes mellitus.

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INTRODUCTION

Neuropathy is a major complication of diabetes mellitus (DM) and is as common as protean. Moreover, it not only leads to an impaired quality of life, but also to an increased morbidity and mortality[1]. Diabetic neuropathy (DN) is the most common form of neuropathy in Western countries, with a wide prevalence in literature, ranging from 5% to 90%[2,3]. Such a large discrepancy is mainly due to the different methods, *i.e.*, sets of electrophysiological and clinical criteria and demographic data adopted[4]. The EURODIAB IDDM Complication Study reports a 28% prevalence of DN across Europe[4]. Considering that DM affects about 246 million people worldwide, it can be estimated that 20-30 million people have a DN[5].

There are numerous and heterogeneous neuropathic syndromes associated with DM. Indeed, the Toronto Diabetic Neuropathy Expert Group[1,6] updated the classification of DNs, providing definitions, minimal criteria for diagnoses and severity estimations. The Toronto Consensus Panels on DN[1,6] accepted Thomas[7] and Boulton *et al*[8]'s separation of DNs into generalized and focal/multifocal neuropathies (Table 1).

Generalized DNs can be further classified into at least two major subgroups, *i.e.*, typical and atypical[1,6]. The most common generalized DN is the typical symmetric sensorimotor polyneuropathy, which is known to be length-dependent[9]. The atypical forms of generalized DN are usually intercurrent, painful varieties and can develop acutely at any time during the course of a patient's disease[10].

Focal and multifocal neuropathies in DM: Entrapment syndromes vs mononeurites/multiple mononeuropathies

The focal and multifocal neuropathies associated with DM can be broadly subdivided into two categories[6], which are characterized by different clinical features and underpinned by various pathophysiological backgrounds. Entrapment of the nerve, favoured by chronic compression, is the pivotal causative factor in the first group: This includes median neuropathy at the wrist (MNW), ulnar neuropathy at the elbow (UNE) and peroneal neuropathy at the knee[6]. The second group encompasses cranial mononeuropathies or mononeurites, multiple mononeuropathies and thoracic, cervical and, most frequently, lumbosacral radiculoplexus neuropathies. The latter is also known as diabetic amyotrophy or Bruns Garland syndrome, where the pathophysiology involves inflammatory factors, microvasculitis and ischemia[11-13]. The 3rd and 6th are the most commonly affected cranial nerves, whilst the 7th is more rarely involved. Some pathological studies have demonstrated a centro-fascicular lesion in the intracavernous portion of the 3rd cranial nerve, sparing the peripheral fibres (and, consequently, the pupillary reaction), attributable to ischemic damage[5,14].

Table 1 Diabetic neuropathies classification (according to Dyck *et al*[6], on behalf of the Toronto Expert Panel on Diabetic Neuropathy, 2011)

Diabetic neuropathies	
Generalized	Typical (symmetrical, lenght-dependent, sensorimotor neuropathy)
	Atypical (painful varieties)
Focal/multifocal	Multiple mononeuropathy
	Entrapment neuropathy
	Lumbosacral/thoracic/cervical radiculoplexus neuropathy

The two groups, *i.e.*, entrapment neuropathies (EN) and mononeuropathies/multiple mononeuropathies, have different clinical characteristics[15]. Indeed, mononeurites or multiple mononeuropathies usually have an acute onset, where pain is a common feature, and a self-limiting clinical course within a 6-mo period, even if forms like diabetic amyotrophy may be highly disabling. On the other hand, EN have a gradual onset, a slow progression and persist without intervention[15].

EN: General epidemiological remarks

EN are remarkably common in DM[15,16] at any stage and may be asymptomatic. Therefore, patients with signs and symptoms suggestive of an entrapment should be thoroughly investigated, as surgery may be indicated[15].

A study by Stamboulis *et al*[17] aimed at establishing whether symptomatic mononeuropathies are more frequent in diabetic patients without symptoms of polyneuropathy than in the general population. A large cohort of 642 consecutive outpatients with various acute symptomatic mononeuropathies (radial, ulnar or peroneal neuropathy, Bell's palsy or median neuropathy at the carpal tunnel) were screened for the presence of DM. The results showed that in 522/642 patients with symptomatic carpal tunnel syndrome (CTS) and in 38/522 with Bell's palsy, DM frequency (7.7% and 10.5%, respectively) did not differ significantly from that expected in the general population[17]. Conversely, the respective DM rates (27.8%, 12.2% and 30.4%) were significantly higher than in the general population in 18 patients with radial neuropathy at (or distally to) the spiral groove[17]. The same finding was observed in 41 patients with ulnar neuropathy and in 23 patients with peroneal neuropathy at the fibular head[17]. This suggests that diabetic patients are more prone to focal limb neuropathies caused by acute external compression. However, this study focused on acute symptomatic mononeuropathies, whilst the majority of EN in DM are chronic and often asymptomatic.

Some cross-sectional and population studies reported a high prevalence of both symptomatic and asymptomatic MNW and ulnar nerve entrapments, with an increased lifetime risk for CTS, compared to the general

population. Herein, we should only like to emphasize that the presence of MNW was detected in 28% of DM patients at diagnosis[18] and that this proportion rose to 62.5% in patients with an average disease duration of 14.5 years[19]. This finding seems to confirm an association between EN, previously reported as not being age-dependent[20], and longer disease duration. Furthermore, subclinical UNE was electro-diagnosed in a remarkably high percentage, *i.e.*, 34%, of DM patients[19], suggesting that the ulnar nerve is very susceptible to focal entrapment in DM, as is the median nerve. These findings and others (see CTS and ulnar entrapments), suggest that EN in DM, mostly at the upper limbs, are not late complications, but rather early neurophysiological abnormalities, where the frequency increases with the disease duration and/or in the presence of generalized DN.

THE PATHOPHYSIOLOGY OF EN: OLD AND NEW EVIDENCE

Epidemiological findings suggest that peripheral nerves are strikingly susceptible to focal entrapment in the presence of DM. Such a liability to chronic compression in DM may be attributable to metabolic factors and endoneurial ischemia, which damage the nerves already in the long preclinical stage[21], as was first proven in animal models[22]. Therefore, a focal EN may be the first and, at times, only manifestation of a peripheral nerve involvement not only in DM, but also in prediabetes.

Growing evidence has shown that, on the one hand, impaired glucose tolerance may cause peripheral neuropathy itself and, on the other, abnormal glucose metabolism underlies a relevant proportion of apparently "idiopathic" sensory neuropathies[23-25]. The effects of sustained impaired glucose tolerance and progressive insulinopenia, also in the absence of hyperglycemia, were studied in an animal model (Goto-KakizaKi rat), which showed a functional and structural neuropathy associated with impaired NGF support and neuropeptide synthesis[26]. Indeed, insulin deficiency has been proven to be a pivotal pathogenetic factor in DN, owing to its unique trophic properties that act on sensory neuron and axon receptors[27]. Not only has it been shown that abnormal direct neuronal insulin signaling contributes to neuro-degeneration, but studies are ongoing on other important molecular factors that influence neuronal and axon growth, such as PTEN (phosphatase and tensin homolog deleted on chromosome 10)[28].

On the other hand, observational studies have reported an increased prevalence of impaired glucose tolerance (up to 34%) in subjects with painful sensory neuropathy[23,24]. In another study, where patients with peripheral neuropathy of unknown origin were administered Oral Glucose Tolerance Test, 56% had abnormal results. Moreover, patients with impaired glucose tolerance had predominantly small fibre neuropathy, compared to those with overt DM, who showed more prominent involvement of large fibres[25]. Hence, some kind of a "continuum" of peripheral nerve damage, associated with glucose dysmetabolism, may be hypothesized. A subtle impairment of nerve function, which begins in the preclinical stage of DM and progresses into the more advanced stages of the disease, is involved in this dysmetabolism, where sustained hyperglycemia alters biochemical pathways in the neurons, making the nerves more susceptible to entrapment.

There is clear evidence of the pathogenetic role the activated polyol pathway plays in diabetic nerves. Both the neurons and Schwann cells of patients with chronic hyperglycemia undergo a shift from the physiologic conversion of glucose into glucose-6-phosphate by hexokinase into an alternative pathway, where excess glucose is transformed into sorbitol by the aldose-reductase. Sorbitol, due to its low plasma membrane permeability, may act as an osmotic driver and, consequently, promote axonal and nerve trunk swelling in DM[29]. Moreover, the activated polyol pathway may induce a decrease in Na/K ATPase activity, leading to intra-axonal Na accumulation and a reduced Na gradient across the plasmatic membrane[30].

Prolonged hyperglycemia may also enhance oxidative stress as radical scavengers are recharged too slowly to counterbalance the higher activity of the electron transport chain induced by the glucose overload[29]. The nerve axons, which are rich in mitochondria, are particularly vulnerable to oxidative damage in DM. Such a "double cellular crisis" of energy failure and oxidative damage has also been proven in Schwann cells[31].

Furthermore, neurodegeneration may also be promoted by advanced glycation end products, which accumulate due to the non-enzymatic glycosylation of proteins and may even damage the function of pericytes and impair the nerve vascular supply[29]. A study on an animal model also led to the hypothesis that endoneurium and perinevrium metabolic and phenotypic abnormalities may be underlying causal factors in the high sensitivity of diabetic nerves to entrapment[32].

The "double crush" hypothesis revisited

All these metabolic alterations lead to both functional impairment and structural changes, mainly swelling, in the nerves, making them more prone to entrapment in anatomically constrained channels[33]. In other words, there is a sort of "two hit" model. The glucose derangement hits the peripheral nerve first, which then becomes more susceptible to a second "hit", by the local factors related to entrapment, such as increased pressure, strain and/or elongation in the anatomically narrow sites. This may well be in agreement with Upton's "double crush hypothesis". In 1973, Drs. Upton and McComas[34] hypothesized in the journal *Lancet* that, if non-symptomatic impairment of axoplasmic flow occurs at more than one site along a nerve, it might well sum-up to cause a symptomatic neuropathy[33,35]. This

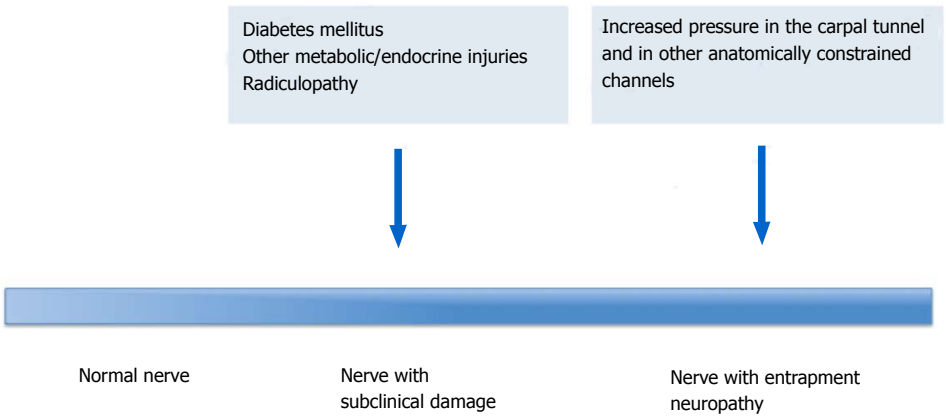

Figure 1 The "Double Crush" hypothesis revisited.

hypothesis relied on the clinical observation that most patients observed by the authors had an MNW, which was often bilateral, or an ulnar neuropathy, associated with cervical radiculopathy. Drs. Upton and McComas[34] supposed that axoplasmic flow could also be impaired by the metabolic damage, based on the frequent association between DM and CTS. Hence, in a revisited and extended "double crush hypothesis" (Figure 1), not only proximal nerve impingement, but also metabolic dysfunction and nerve swelling subsequent to DN, may be involved in the "first crush". This predisposes nerves to chronic compression, *i.e.*, the "second crush", in anatomically constrained sites, like carpal and/or tarsal tunnels[15].

This mechanism seems to be consistent with the frequent association of both generalized and focal DN, where an EN is superimposed on a generalized form of DN. Indeed, the metabolic derangement and the microvessel alterations, subsequent to chronic hyperglycemia, lead to exhaustion of the ATP supply and an earlier fibre dissolution in the distal nerve compartment[36]. This may be in line with the well-known dying-back pathophysiological mechanisms that underlie generalized typical, symmetrical, length-dependent diabetic neuropathy. However, the same subclinical damage to distal nerve segments and the early demyelination of small sensory fibres may be taken into account when interpreting a slow conduction velocity and/or conduction blocks across the carpal tunnel, in the distal median nerve in MNW, which is often the earliest EN.

Diabetic neuropathy: Axonal or demyelinating?

The question thus arises whether the nature of DN is axonal or demyelinating. The results of a study aimed at answering this question[37] suggested that both mechanisms are involved. Demyelination seems to appear earlier in diabetic patients with or without symptoms of polyneuropathy, whilst axonal loss seems prevalent in more advanced DN, where it may be responsible for most of the symptoms. Moreover, the abnormal conduction velocity in the distal segment of the sural nerve, observed by Cappellari *et al*[38] in impaired glucose tolerance subjects without clinical neuropathy, also suggests that the myelin dysfunction of the distal sensory fibres represents the earliest detectable nerve response to hyperglycemia. Furthermore, a peculiar pattern of "abnormal median or ulnar/normal sural", *i.e.*, reduced sensory action potential of median or ulnar nerve in the presence of normal sensory action potential of sural nerve, was detected in 82% and 80% respectively of newly diagnosed diabetic patients[18]. Such a peculiar pattern was found in a high proportion of patients with acute inflammatory polyneuropathy and was thus considered suggestive of an early distal nerve involvement[39]. Hence, if the small myelinated nerve fibres may be assumed to be the most susceptible to entrapment, this may explain the finding of median neuropathy in a very distal segment of the nerve across the carpal tunnel, as the earliest neurophysiological alteration in patients with abnormal glucose metabolism (impaired glucose tolerance and DM). This is observed even in the absence of an overt DN. On the other hand, demyelination has been described as the first human nerve response to chronic compression in the pioneering studies carried out by Dellon *et al*[22] and Mackinnon *et al*[40], who detected markedly thinner myelin after compressive injuries. A Schwann cell proliferation, accompanied by increased apoptosis, has also been observed in animal models some weeks after compression[41]. These and other experimental findings reviewed by Tapadia *et al*[41], suggest that myelinated neurons may be particularly susceptible to mechanical stress, a pivotal factor in EN. Therefore, in the presence of a DN the peripheral nerves, that are already suffering from endoneurial ischemia and altered axonal excitability, are made more vulnerable to pressure.

This may lead, on the one hand, to an induction of demyelination and, on the other, cause local vascular impairment and superimposed axonal damage in anatomical tunnels[42]. This seems to imply that, in EN, once an entrapment has occurred, the chronic compression may enhance the pre-existing nerve metabolic damage within a sort of vicious circle, leading to

worsening, unless surgery is performed. Furthermore, regeneration is impaired in DM patients. Indeed, the microangiopathic changes in small vessels, the metabolic derangement of neurons and Schwann cells, defects in the inflammatory cells within the injury milieu and lack of trophic factors, may contribute to the failure of regenerative programmes[43].

EN: Often asymptomatic

Another peculiar finding of EN in DM deserves mention. It is well known that DN are often asymptomatic. Indeed EN, mainly MNE and UNE, may frequently occur as subclinical neurophysiological alterations, in the absence of clinical symptoms, as demonstrated by some studies[18,19,44,45]. MNW was asymptomatic in 36% of the patients in a cohort of some newly diagnosed DM patients[18], similar to that obtained by Celiker *et al*[44]. This suggests that the presence of lesions in the proximal nerve segment and/or an alteration of the threshold of the sensory nerve fibres may render patients with DN less prone to develop a clinically evident CTS than normal controls[18,20,44,45].

EN DIAGNOSIS: GENERAL METHODOLOGICAL ASPECTS

Electro-diagnostic studies are the mainstay in the diagnostic work-up of EN. Sensory and motor conduction studies provide an array of documentation on neuropathy. They distinguish the generalized forms from focal forms and show focal neurophysiologic abnormalities in anatomically constrained channels along the suspected nerve. Moreover, electrodiagnostic studies allow for the demonstration of the axonal or demyelinating features of the neuropathy, the staging of its severity and, last but not least, the exclusion of other concomitant diseases. One remarkable characteristic of electromyography is that it is able to detect a superimposed radiculopathy (such as a cervical C7-C8 radiculopathy concomitant with CTS) in the aforementioned "double crush" syndrome[34].

There is growing evidence in favour of the use of imaging techniques as ancillary or complementary methods in the diagnostic process of neuropathies, above all for EN. Ultrasonography has been proven to offer several advantages in assessing peripheral nerves, including its cost-effectiveness, time-efficient evaluation of long nerve segments, ability to perform dynamic maneuvers, lack of contraindications, portability and non-invasiveness[46]. The last decade has witnessed an extensive use of neuromuscular ultrasonography, particularly in the assessment of EN, where the most common and reproducible sonographic finding is nerve enlargement, just proximal to the site of entrapment[47]. This enlargement is typically fusiform, rather than discretely focal, and is usually measured by the nerve cross-sectional area. Although the cause of nerve enlargement has not yet been completely clarified, it has been hypothesized to be the result of axoplasmic damming, as observed in entrapment and chronic nerve compression models[47]. Moreover, inflammatory and/or vascular components may contribute to nerve enlargement. Along with nerve enlargement, just proximal to the site of entrapment, other less common findings have been reported and include hypoechoic nerve echo-texture, nerve flattening and pinching at the entrapment site, enlargement of single or multiple fascicles and/or increased vascularity within the nerve[47]. A recent study[48] was carried out to identify ultrasound findings in type Ⅱ DM patients complaining of neuropathic symptoms and signs. Nerve ultrasound revealed an increased cross-sectional area in the peripheral nerves both at compression sites, even in the absence of clinical symptoms, and at non-compression sites. The authors hypothesize that cross-sectional area enlargement at compression sites indicates subclinical nerve damage and probably susceptibility to entrapment. Whilst cross-sectional area increase at non-compression sites suggests early morphological abnormalities, even when nerve conduction studies are unremarkable[48]. However, further studies should be carried out to confirm these results and to identify any correlations between ultrasonographic and electrodiagnostic findings.

The current role of magnetic resonance imaging (MRI) neurography in diabetic neuropathy is mainly that of excluding the presence of a lesion as the cause of nerve entrapment in cases of focal or regionally distributed multifocal neuropathy, mostly when clinical and electrodiagnostic findings are inconclusive. Furthermore, MRI neurography can diagnose those extra-neural affections that mimic neuropathic symptoms, such as Charcot arthropathy, osteomyelitis, plantar fasciitis, *etc*[49].

MEDIAN ENTRAPMENT NEUROPATHY AT THE WRIST AND CARPAL TUNNEL SYNDROME

Median nerve entrapment neuropathy at the wrist (MNW) is the prototype of EN and is caused by the compression and traction of the median nerve within the carpal tunnel, an osteofibrous outlet located between the transverse carpal ligament and the carpal bones. It may be asymptomatic or accompanied by sensory complaints (pain, numbness, paraesthesias) or motor symptoms (weakness, clumsiness) in the section of the hand supplied by the median nerve. CTS is the commonest median neuropathy, with a 10% lifetime risk in the general population[50]. Prevalence rates vary widely across studies, depending on various factors, such as the geographic area, age, anthropometric data, exposure to risk factors for CTS and the diagnostic criteria used. Recently, a CTS prevalence of 2.3% to 4.3% has been reported in two large cohorts of French workers[51]. Some studies[18-20,42,52] report the prevalence

of both MNW and CTS to be several-fold higher in DM patients than in the general population, above all in DM patients with polyneuropathy and/or long disease duration. CTS has been detected in 14% of diabetic subjects without polyneuropathy and in 30% of subjects with polyneuropathy[42]. Moreover, an MNW was found in 28% of newly diagnosed DM patients, compared to 62.5% of patients with an average disease duration of 14.5 years[18,19]. Similar results were reported in another study carried out on 146 DM patients, where CTS was diagnosed in 39% of the sample, 28% of males and 46% of females[53]. The risk of hand syndromes, including CTS, stenosing flexor tenosynovitis and Dupuytren disease, was evaluated in a population-based cohort study (606152 diabetic patients and 609970 matched for age and gender)[54], where the hazard ratio for CTS was: 1.31 (95%CI: 1.28-1.34) in DM patients. In the longitudinal Fremantle Diabetes Study, aimed at determining the incidence and predictors of carpal tunnel decompression in 1284 DM patients, the incidence of CTS was 5.5 cases per 1000 patient-year, at least 4.2-fold that of the general population[52]. In a previous review, aimed at evidencing any increase in the prevalence of specific conditions in CTS patients, a two-fold increased risk (OR = 2.2; 95%CI: 1.5-3.1) for DM was detected[55]. Therefore, DM is an independent risk factor for CTS[55]. A surprisingly high lifetime risk of CTS has been reported in type 1 DM patients, where it may rise to 85% after 54 disease years[56].

A case-control Italian study[57] reported that, not only overt DM, but also abnormal glucose metabolism was present in a high percentage of the subjects with idiopathic CTS. This finding led the authors to propose insulin resistance screening for all patients with CTS, as they found insulin resistance in 80% of patients: 45% had impaired glucose tolerance, 14% newly diagnosed DM and 20% insulin resistance only[57].

The dominant hand is the most commonly affected in CTS, with a prevalence for females, where the tunnel tends to be smaller, and in obese DM patients[53,58].

Such a strong association between MNW/CTS and DM is underpinned by the fact that DM nerves are very prone to compression due to metabolic and vascular factors occurring in a DM already in the preclinical stage. Indeed, increased pressure in the carpal tunnel, which rises up to 8-10-fold in the flexion/extension movements of the wrist, and nerve traction may reduce the intra-neural microcirculation, damage the myelin sheath and the axonal function, as well as the connectival structures, in a vicious circle where the nerve swelling, due to oedema and hypoxia, are a pivotal aggravating factor in the pathophysiology of CTS[59] (Figure 2).

Median nerve entrapment in the carpal tunnel with neural mobilization during anatomical stress may lead to conduction failure also in the non-diabetic population. This has recently been demonstrated by a study where recruitment properties of the median nerve were studied by the stimulus-response curve before and after intermittent-repetitive neural mobilization,

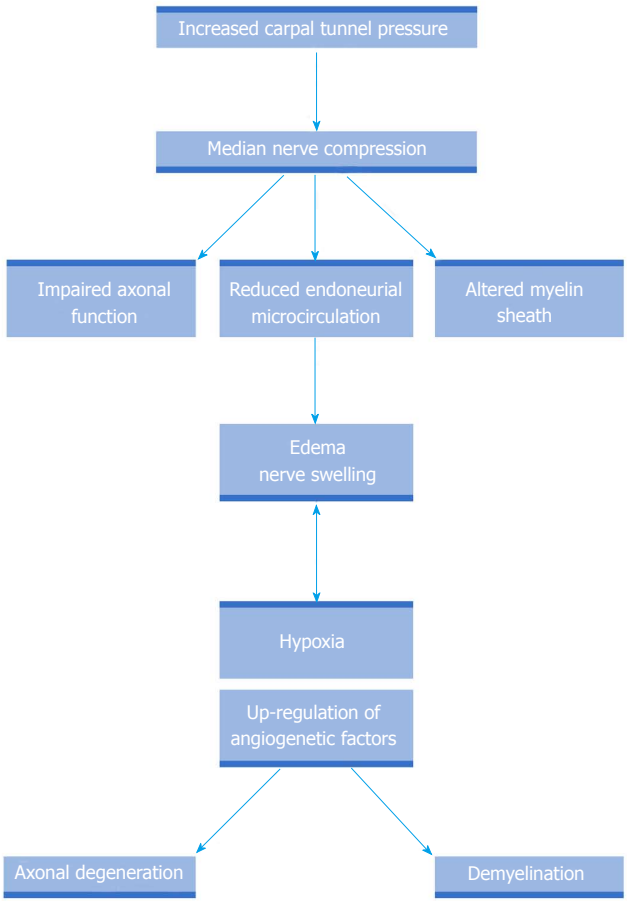

Figure 2 Carpal tunnel pathophysiology (modified from Aboonq[59], 2015).

in subjects with and without CTS[60]. Only subjects with CTS exhibited a strikingly abnormal stimulus-response curve. This finding suggests that compressive forces may alter energy-dependent processes during anatomical stress in elongation, leading to conduction block in axons[60]. Taken as a whole, these findings do seem to imply that once an entrapment has occurred in MNW/CTS, anatomical stress may enhance the pre-existing metabolic and ischemic nerve damage within a sort of vicious circle, leading to axonal degeneration and to a worsening of the entrapment, unless surgery is performed.

When the severity of an electrophysiologically confirmed CTS was compared between patients with DM (and no concomitant metabolic syndrome) and patients with metabolic syndrome, it was observed to be more severe in those with a metabolic syndrome[61]. This finding suggests the presence of other disease modifying factors related to the metabolic syndrome.

Nerve conduction studies are the mainstay in the diagnostic approach to the MNW and CTS. Although quantitative sensory testing for the different modalities (temperature, pain, vibration perception threshold, perception testing) may be more sensitive than standard clinical tests[62], it has considerable subjective components making it unreliable for diagnosis[15,63].

Electrophysiological studies, that measure median nerve sensory and motor conduction parameters, not

only allow for a diagnosis of MNW, but also the staging of its severity, as they may detect focal abnormalities within the carpal tunnel itself. The techniques for an electrodiagnosis of CTS were described and assessed by Werner *et al*[64], in an American Association of Neuromuscular and Electrodiagnostic Medicine monograph. The sensory response is particularly useful to diagnose CTS, as sensory fibres have a larger proportion of large myelinated fibres, with a higher energy requirement, that are more susceptible to ischemic and metabolic damage. Comparison of the median nerve sensory latency with ulnar or radial latency has been demonstrated to be more effective than the use of absolute median nerve latency in documenting the median nerve entrapment within the carpal tunnel[64].

An electrodiagnosis of CTS may be particularly challenging in DM patients with a polyneuropathy, where the comparative tests between the ulnar and radial nerve may necessitate that the values be adjusted from those used in the general population to more conservative cut-off values[64]. Moreover, segmental and comparative median nerve conduction tests (the disto-proximal latency ratio) showed a high sensitivity of 90% in DM patients affected by polyneuropathy, which is similar to that of the median-ulnar sensory latency to digit 4 comparison[65].

The measures needed to achieve a minimum standard of care for the use of electrodiagnostic testing in the suspicion of a CTS have been defined according to the guidelines developed by the American Association of Neuromuscular and Electrodiagnostic Medicine[66].

MNW is the entrapment neuropathy most frequently studied with ultrasonography. Enlargement of the median nerve cross-sectional area at the distal wrist crease is an accurate parameter for the diagnosis of CTS, with a sensitivity and specificity of > 85% in several studies[47]. The median nerve has a lower mobility in patients affected by CTS than healthy controls and this decreased range of movement can be quantified in both lateral and distal-proximal planes, according to set grading scales[47]. A recent study[67] suggests that ultrasonography be used to make a differential diagnosis between EN and diabetic neuropathy in DM patients. There was a wider median nerve cross-sectional area in DM patients with polyneuropathy than in controls, in particular in the CTS subgroup, where there was a larger cross-sectional area at the wrist and wrist-to-forearm[67].

The treatment of CTS is mainly surgical, aimed at decompression of the median nerve by sectioning the carpal transverse ligament. Surgical nerve release can be done either by an open approach (OCTR) or endoscopically (ECTR). Although the two approaches differ only slightly as to pain relief and improvement of functional status, there may be a functionally significant benefit of ECTR over OCTR in improving grip strength[68]. Several non-surgical approaches, including oral steroids, splinting, ultrasound, yoga and carpal bone mobilization, have been suggested for patients with mild-moderate symptoms, with significant short-term benefit, although long-term efficacy remains to be ascertained[69]. In the DM population, where the metabolic derangement may impair nerve regeneration[43], the question arises whether the treatment, above all surgery, would maintain the same long-term efficacy as it does in the general population. Such a question has been addressed by some studies. The outcome of CTS surgical release was evaluated at one month and one year in DM patients and was observed to be inferior and slower than in non-diabetic controls[70]. Such a difference was attributed to metabolic factors and impaired nerve regeneration, which are likely to be responsible for the slower recovery in DM patients[70]. A worse surgical outcome was reported at 10 post-surgical years for DM patients with CTS, compared to idiopathic CTS patients[71]. However, another recent study was carried out on 35 patients and 31 normal controls with a 5-year follow-up. It reported that after surgical release of CTS, DM subjects had a long-term improvement in sensory, motor function and cold intolerance, comparable to that of non-diabetic controls[72]. Interestingly, the improvement in cold intolerance would be consistent with a potential for long-term regeneration of small fibers[72]. Thomsen *et al*[73] also assessed the neurophysiologic recovery after carpal tunnel release in the same sample of DM patients, who had significantly impaired nerve conduction parameters, both before and after surgical carpal tunnel release, compared to non-diabetic patients. Nevertheless, neurophysiologic recovery after carpal tunnel surgery did not differ between the two patient groups or between diabetic patients, with or without peripheral neuropathy. Thus, relevant neurophysiologic impairment of the median nerve, or signs of peripheral neuropathy, is not likely to preclude significant recovery after carpal tunnel release in DM patients[73]. Even the quality of life, evaluated with generic and disease-specific questionnaires (SF-36 and Boston Carpal Tunnel Questionnaire, respectively), that was more impaired in DM CTS patients than in non-diabetic CTS subjects and the general population, had the same post-surgical scores for both DM and non-diabetic patients[74]. Therefore, the authors stated that DM patients should be given the same surgical option for CTS treatment as non-diabetic patients[73,74].

UNE AND ULNAR ENTRAPMENT NEUROPATHY AT THE WRIST (UNW)

The second most frequent entrapment neuropathy involves the UNE, in the retroepicondylar groove or under the humeroulnar aponeurotic arcade, *i.e.*, the cubital tunnel. A study by Mondelli *et al*[75] investigated the UNE incidence in the general population, where there was a crude incidence of 24.7 per 100000 person-years and a standardized incidence of 20.9 per 100000 person-years. A prospective study[76] was carried out on a group of subjects with suspected UNE given electrodiagnostic and ultrasonographic examination.

It reported that the entrapment was localized in the retroepicondylar groove in 76% of the cases, where it was mainly demyelinating and at the humeroulnar aponeurotic arcade in 17%, where it was mostly axonal. UNE may occur without symptoms or be accompanied by painful paraesthesias in the fourth and/or fifth digit or by hypothenar or interosseus muscle weakness and wasting.

Clinical and neurophysiologic findings of a severe ulnar neuropathy were previously reported in a group of patients affected by DM with severe systemic complications[77]. Another four patients with type I DM and clinical findings suggestive of severe ulnar neuropathy have been described, where nerve conduction studies detected a partial conduction block or abnormal temporal dispersion within the forearm segment of the ulnar nerve, along with a mild underlying polyneuropathy[78]. The authors raised the question whether the UNE was due to an increased propensity to focal compression of the ulnar nerve within the humeroulnar arcade, or whether it represented a localized manifestation of the generalized polyneuropathy[78]. According to the advances made in DN pathophysiology, this seems to be only an apparent contradiction, in as much as, in reality, the metabolic derangement of diabetic nerves may underpin their remarkable liability to compression.

A more recent study[19] assessed the prevalence and electrophysiological features of ulnar entrapment neuropathy, according to the American Association of Electrodiagnostic Medicine protocol[79]. A cohort of 64 consecutive DM patients were studied and UNE was electrodiagnosed in 34% (18% were not polyneuropathic); UNW was detected in 11% of this sample[19]. On the basis of such a high proportion of patients (45%) with neurophysiological alterations consistent with ulnar EN at both sites (elbow and wrist), the authors concluded that the ulnar nerve, similarly to the median nerve, is very susceptible to focal entrapment in DM. Moreover, they suggested that upper limb sensory and motor NCS, including motor conduction velocity across the elbow, be routinely evaluated in the staging of DM patients[19].

Furthermore, the frequent neurophysiological abnormalities detected on the ulnar nerve by this electrodiagnostic study[19] were mostly asymptomatic and only a small proportion of patients with a diagnosis of UNE showed the clinical signs of EN. This finding that UNE was mainly subclinical is in agreement with previous evidence related to MNW, which was asymptomatic in one third of DM patients[18,20,44,45]. It is also in line with the hypothesis that there is an alteration of the threshold of the sensory nerve fibres in DM and this may well explain the lower propensity for DN patients to develop a clinical symptomatology[18,20,44,45].

Furthermore, in the same study[19], UNW was concomitant with MNW in all but one case. Indeed, the question arises as to the association between UNW and MNW, where the discrepancy in literature is most likely to be due to the different methods adopted[80]. Indeed, in DM patients, where the frequency of MNW is high, concomitant involvement of Guyon's canal (UNW) has been shown to reduce the sensitivity of the median-ulnar comparative studies[81]. Therefore, the neurophysiological diagnosis of concomitant CTS and UNW may present a challenge, above all in DN patients. A retrospective case-control study[82], carried out on an electrodiagnostic database, included 1924 patients evaluated for CTS and 1024 DM patients investigated for CTS and/or polyneuropathy. A logistic regression analysis showed that the presence of CTS was associated with a two-fold risk of UNW in both idiopathic CTS and DM CTS groups. These finding suggest that the presence of concomitant UNW and CTS should be carefully pursued in nerve conduction studies, above all in DM patients.

A study by Mondelli *et al*[75] compared the prevalence of DM in two consecutive samples of patients with UNE and CTS and reported that it was remarkably similar, *i.e.*, 6.0% and 6.6% respectively. Indeed, patients with UNE and DM were clinically and neurophysiologically indistinguishable from other UNE patients (both idiopathic and post-traumatic). The only difference was a smaller amplitude of the sensory response in the DM patients, which may well be attributable to the underlying axonal polyneuropathy[75]. These findings strengthen the similarities between median and ulnar EN in DM, which obviously act in the same way on peripheral nerves at both the upper and lower limbs, predisposing them to compression in anatomically narrow sites, were the nerves are exposed to increased pressure and repetitive strain.

EN AT THE LOWER LIMBS

It seems that entrapments of the ulnar and median nerve are not only a typical electrophysiological feature of polyneuropathy in DM, but also the early subclinical sign of peripheral nerve damage, even when a generalized diabetic neuropathy is not yet evident. Whilst EN at the lower limbs seem to be less frequent feature of DM. Indeed, the evidence of an increased frequency of common peroneal nerve entrapment in DM at the level the fibular head and of the tarsal tunnel syndrome is less overwhelming, compared to upper limb focal neuropathies.

In the past it was reported that DM was the underlying cause of peroneal neuropathy in only 5%-12% of patients[83]. However, a more recent study was carried out to determine whether peripheral neuropathy could explain the apparent association between DM and disability in ageing subjects. It reported that reduced peroneal motor response amplitude at multiple sites and weakness of foot dorsiflexion were found in two thirds of the sample of DN patients over 65[15,84].

A similar impairment of peroneal nerve conduction parameters was observed in subjects 65 years or older in a study[85], carried out to determine whether DM was associated with objective measures of physical and

peripheral function. It concluded that DM patients had a decreased conduction velocity and motor response amplitude at the lower limbs, along with a reduced walking speed, compared to the non-diabetic subjects[85]. However, if direct neurophysiological signs of entrapment, *e.g.,* conduction block or reduced motor conduction velocity across the fibular head, are not carefully searched for and detected, peroneal axonal damage may be consequent to DN itself or to an L5 radiculopathy or a lumbar spinal stenosis. These conditions may even be superimposed on DN, making for a complex differential diagnosis.

The diagnosis of tarsal tunnel syndrome is even more challenging, as it is characterized by entrapment of the tibialis nerve as it curves behind the medial malleolus underneath the flexor retinaculum. There may be a selective or prevailing entrapment of the medial or lateral plantar nerves, two of the terminal branches of tibial nerve, in a tarsal tunnel syndrome. Indeed, this is more difficult to demonstrate without the adoption of a complex electrodiagnostic protocol with segmental analysis of the motor conduction velocity in the distal tracts of the tibial nerve[86]. Such shortcomings in neurophysiological investigation protocols seem to be common to several studies on neuropathy at the lower limbs in DM, making them unreliable when investigating entrapment. Therefore, these methodological limits could be considered a plausible explanation for the less detailed evidence on entrapment in the lower limbs, than what is available for the upper extremities in the general population and even more so in DM patients. Indeed, similarities between CTS and tarsal tunnel syndrome might be expected as they have a common pathophysiological background that predisposes the nerves to external compression.

Surgical nerve release seems to find a rationale in the "revisited" Upton and McComas's "double crush" hypothesis (Figure 1)[15,34], where DN (with nerve swelling) represents the "first crush" and nerve compression at the tarsal tunnel or peroneal head the "second crush"[87], despite the often limited electrodiagnostic evidence for entrapment superimposed to the length-dependent DN. This hypothesis has received recent support by nerve ultrasonography that demonstrated an increased cross-sectional area in nerves affected by neuropathy[47]. Moreover, ultrasound imaging was used to quantify the magnitude and timing of tibial nerve excursion during ankle dorsiflexion in patients with DM and was compared to matched healthy controls[88]. The results showed that the nerve cross-sectional area was increased at the ankle in the DM group, where the tibial nerve longitudinal excursion at the ankle and knee was reduced proportionally to the severity of neuropathy. Moreover, on the basis that a larger tibial nerve size within the tarsal tunnel in patients with DM may restrict longitudinal excursion, it has been hypothesized that such altered tibial nerve biomechanics may be related to painful symptoms during functional activities[88].

Surgical decompression of nerves at the lower limbs

Several studies have been based on the "double crush" hypothesis (Figure 1), from the pioneering work by Dellon[89] to more recent studies[90,91], which evaluated the efficacy of surgical decompression in DN patients. Considering Valdivia Valdivia *et al*[90]'s retrospective review, the results of neurolysis on multiple sites of chronic nerve compression in the lower extremity were analyzed in 158 consecutive patients, 96 with DM and 62 with idiopathic neuropathy. A significant post-operative improvement was reported in sensation and balance at a minimum follow-up of 1 year; even pain improved, as demonstrated by a decrease in the Visual Analogic Scale score. There was no statically significant difference in outcomes between patients with DM *vs* idiopathic neuropathy in response to nerve decompression[90]. Another study by Liao *et al*[91] investigated into the effect surgical decompression had on painful DN as to the pain distribution, where a total of 306 patients, with painful diabetic lower-extremity neuropathy were treated with Dellon surgical nerve decompression. Patients had pre- and post-surgical (were appropriate) clinical evaluation and high-resolution ultrasonography (cross-sectional area), as well as nerve conduction studies (tibial and common peroneal nerve conduction velocity). Surgical patients were retrospectively assigned into two subgroups, *i.e.*, focal and diffuse pain, according to the distribution of the diabetic neuropathic pain. The control group included 92 non-surgical patients with painful DN. After surgical decompression, the surgical group had a higher reduction in pain (measured as Visual Analogic Scale score) and an improvement in nerve conduction and cross-sectional area than did the control group. As was expected, based on the rationale on the surgical decompression approach, a greater improvement in Visual Analogic Scale and cross-sectional area was observed in the focal pain group than in the diffuse pain group. The authors concluded that decompression of multiple lower-extremity peripheral nerves was effective in patients with painful DN to a greater extent in patients with focal symptoms[91].

However, unfortunately, these two studies show relevant methodological shortcomings. Firstly, there was no demonstration of a precise site of entrapment by direct electrodiagnostic signs along nerves, which showed only axonal damage subsequent to DN. Furthermore, serial measurements of nerve motor conduction velocities may show a variability[92] which was not taken into account in the post-surgical evaluation of the improved conduction velocity along tibial and common peroneal nerves. In addition, most of the outcome measures evaluated by these studies are subjective, making the definition of focal pain in the study of Liao *et al*[91], 2014 questionable. Therefore, we are of the opinion that further neurophysiological studies should be carried out in an effort to better characterize EN superimposed on DN at the lower limbs. Moreover, further prospective studies, based on detailed

electrodiagnostic and ultrasonographic protocols aimed at localizing the sites of nerve compression are welcome to better assess the efficacy of surgical nerve decompression in patients suffering from painful DN.

CONCLUSION

EN are so common in DM, at any stage, that they may considered a neurophysiological hallmark of peripheral nerve involvement in DM. Indeed, EN, particularly in the upper limbs, may represent the earliest neurophysiological abnormalities, which are often asymptomatic, even in the absence of a generalized polyneuropathy or, usually later in the natural history of DM, they may be superimposed on a generalized DN.

The remarkable frequency of EN in DM is underpinned by a peculiar pathophysiological background. The peripheral nerves, due to the metabolic alterations consequent to altered glucose metabolism, even in the preclinical stage, show both functional impairment and structural changes, mainly swelling, which makes them more prone to entrapment in anatomically constrained channels. The diagnosis of EN relies mainly on nerve conduction studies and may sometimes be challenging, mostly in DM patients with a generalized polyneuropathy. Despite this, we believe that an EN diagnosis is a must, not only for the staging of DM, but also due to the fact that the treatment of choice for numerous EN cases may have to be surgical.

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REVIEW

Update on the treatment of type 2 diabetes mellitus

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Abstract

To achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Achieving near-normal glycated hemoglobin significantly, decreases risk of macrovascular and microvascular complications. At present there are different treatments, both oral and injectable, available for the treatment of type 2 diabetes mellitus (T2DM). Treatment algorithms designed to reduce the development or progression of the complications of diabetes emphasizes the need for good glycaemic control. The aim of this review is to perform an update on the benefits and limitations of different drugs, both current and future, for the treatment of T2DM. Initial intervention should focus on lifestyle changes. Moreover, changes in lifestyle have proven to be beneficial, but for many patients is a complication keep long term. Physicians should be familiar with the different types of existing drugs for the treatment of diabetes and select the most effective, safe and better tolerated by patients. Metformin remains the first choice of treatment for most patients. Other alternative or second-line treatment options should be individualized depending on the characteristics of each patient. This article reviews the treatments available for patients with T2DM, with an emphasis on agents introduced within the last decade.

Key words: Type 2 diabetes mellitus; Treatment; Oral antidiabetic agents; Injectable antidiabetic agents; Older people; Renal impairment; Future treatments

Core tip: To achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Physicians should be familiar with the different types of existing drugs for the treatment of diabetes and select the most effective, safe and better tolerated by patients. This article reviews current and future treatments for patients with type 2 diabetes mellitus, its use in clinical practice and in special situations such as kidney failure and elderly patient, with an emphasis on agents introduced within the last decade.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a disease that affects more than 400 million people around the world. In 2040, there will be more than 640 million people with diabetes worldwide[1]. The prevalence of T2DM is expected to double within the next 20 years, due to the increase of the age, obesity and the number of ethnic groups of high risk in the population[2], with significant increases in cardiovascular disease[3], end-stage renal disease (ESRD)[4], retinopathy and neuropathy. Additionally, to achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Achieving near-normal glycated hemoglobin (HbA1c) significantly decreases risk of macrovascular and microvascular complications[4]. However, only about 50% of diabetic patients reach their HbA1c target[5]. Algorithms for the treatment of diabetes highlight the need for good glycaemic control to reduce the development or progression of diabetes complications. In recent years has increased the number hypoglycaemic agents available for the treatment of T2DM. A recent position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on a patient-centered approach in the management of patients with T2DM[6] gives an overview on how different conditions and co-morbidities may influence the choice of different hypoglycaemic agents. The ADA/EASD suggests that initial intervention should focus on lifestyle changes. Moreover, changes in lifestyle have proven to be beneficial[7], but for many patients is a complication keep long term, due to differing experiences or perceptions[8]. In general, drug therapy includes not only initial hypoglycaemic agents, but other intensification strategies to maintain glycaemic control over time, often requiring several drugs with different mechanisms of action[9]. Physicians should be familiar with the different types of existing drugs for the treatment of diabetes and select the most effective, safe and better tolerated by patients.

This article reviews current and future treatments for patients with T2DM, its use in clinical practice and in special situations such as kidney failure and elderly patient, with an emphasis on agents introduced within the last decade. The aim of this review is to perform an update on the benefits and limitations of different drugs, both current and future, for the treatment of T2DM.

LIFESTYLE CHANGES

Dietary intake and physical exercise are the two main determinants of the energy balance[10], and they are considered as a basic base in the treatment of patients with diabetes. Adequate rest is also very important for maintaining energy levels and well-being, and all patients should be advised to sleep approximately 7 h per night[9]. Evidence supports an association of 6 to 9 h of sleep per night with a reduction in cardiometabolic risk factors[11], whereas sleep deprivation aggravates insulin resistance, hypertension, hyperglycaemia, and dyslipidaemia[12]. On the other hand, a screening of patients with suspected obstructive sleep apnoea should be performed, and refer them to a sleep specialist for evaluation and treatment[9].

Although the pharmacological options are each time more extensive and they offer more therapeutics possibilities, especially in the T2DM, the interventions in the life style are essentials in the approach of these patients and they are needed to get the therapeutics goals[13].

Table 1 Classification of degree of obesity by body mass index

Body mass index (kg/m^2)	
Normal weight	18.5-24.9
Overweight grade 1	25-26.9
Overweight grade 2	27-29.9
Obesity grade 1	30-34.9
Obesity grade 2	35-39.9
Obesity grade 3 (morbid)	40-49.9
Obesity grade 4 (extreme)	⩾ 50

Adapted from World Health Organization (WHO) 1995, WHO 2000 and WHO 2004.

Diet

When nutritional intervention is contemplated, the co-morbidities that can coexist in a diabetic patient also have to be considered. The recommendations on dietary aspects can contribute to achieve the desired blood glucose, blood pressure, lipid profile and weight[10,14], as well as improve sleep apnoea, depression and quality of life related to health; in addition, it has been observed that the incidence of urinary incontinence in women is reduced[15-18].

Numerous randomized controlled trials have demonstrated the metabolic benefits of nutritional recommendations in reducing HbA1c; being variables the results got depending mainly on the length of the disease[19,20].

Energetic contribution: Total caloric intake diet will depend on several factors, being determining the presence of overweight or obesity. Body mass index (BMI) is a tool commonly utilized in clinical practice to classify patients and it is calculated by the following equation: [weight (kg)/height (m^2)] (Table 1).

Most T2DM patients have some degree of overweight or obesity[21]. It has been connected to insulin resistance and defects in insulin secretion. These

Table 2 Different formulas for calculating baseline energy needs of people

Harris-Benedict equation[1]
Males: BMR (kcal/d) = 66 + 13.7 × weight (kg) + 5 × height (cm) - 6.8 × age
Females: BMR (kcal/d) = 655 + 9.6 × weight (kg) + 1.8 × height (cm) - 4.7 × age
Mifflin St Jeor equation[2]
Males: BMR (kcal/d) = 10 × weight (kg) + 6.25 × height (cm) - 5 × age + 5
Females: BMR (kcal/d) = 10 × weight (kg) + 6.25 × height (cm) - 5 × age - 161

[1]Harris JA, Benedict FG. Proceedings of the National Academy of Sciences of the United States of America. *Nutr Rev* 1918; **4**: 370-373. [2]Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. *Am J Clin Nutr* 1990; **51**: 2241-2247. BMR: Basal metabolic rate.

Table 3 Glycaemic index, glycaemic load and carbohydrates portion

GI: Observed increase in blood glucose after eating 50 g of a food, compared with the observed increase after intake of 50 g of white bread or glucose
Glycaemic load: GI × total amount of carbohydrates (grams) of the usual food portion
Carbohydrates portion: amount of food containing 10 g of carbohydrates

Glycaemic Research Institute. Available from: URL: http://www.glycemic.com/GlycemicIndex-LoadDefined.htm. GI: Glycaemic index.

alterations favour the appearance and worsening of diabetes[22], so in these cases in addition to an adequate distribution of macro and micronutrients, we should look for as a main objective a weight reduction by reducing the caloric intake. To achieve this objective, it has been proposed that the caloric intake of the diet prescribed to a diabetic patient with obesity should contain between 500 and 1000 kcal less of its energy needs[23]. This weight reduction will improve the insulin sensitivity, being a favourable factor to improve the glycaemic control parameters[24]. In the case of patients for whom there is no excess weight, the diet should be isocaloric.

There are different formulas for calculating baseline energy needs of people (Table 2). To these basal needs, a factor depending on the physical activity must be added. The randomized trial LOOK AHEAD, showed that weight loss after an intervention in lifestyles, improve blood pressure, and blood glucose control and lipid profile[25], especially in patients with a recent diagnosis of disease[3]. When this study was prolonged, it was found that intensive nutritional intervention did not provide an improvement in the rate of cardiovascular events or weight loss when it is compared against a standard nutritional intervention[26].

Macronutrient distribution: There is not enough evidence to suggest an ideal percentage in the distribution of carbohydrates, lipids and proteins. There are several studies that have sought to distribute the best ratio macronutrients without finding valid results, and several dietary patterns that have been analysed as the Mediterranean diet, vegetarian or vegan diet, Dietary Approaches to Stop Hypertension (DASH), low-fat diet and low carbohydrates diet observing a modest effectiveness of managing diabetes. The benefits happen only when they are accompanied by a lose weight so more studies are needed[27].

Carbohydrates: Although there is no consensus on the percentage of carbohydrates that people with diabetes should eat, it has been shown that the amount and the type of carbohydrates are the main determinants for glycaemic control. Counting carbohydrates has proven to be very important in all patients. It allows a better adjustment of the postprandial blood glucose for those who take insulin. With this method, patients consumed a known amount of carbohydrates divided among different meals and calculated it in grams of carbohydrates per portion (Table 3). This type of measurement is more important in patients with basal-bolus treatment or with continuous insulin infusion[28].

It is preferable that the intake of carbohydrates comes from products such as fruits, vegetables, legumes, whole grains and dairy *vs* those involve the added contribution of salt, fat or simple sugars[10].

Index and glycaemic load: There is large confusion in the interpretation about the effect of the diet with low glycaemic index and there is not unanimity in the results of the different studies. Even though these diets are recommended by some associations because there are studies in which have been observed a better glycaemic control when it is compared above all with high glycaemic index food[29], there are articles that have questioned this assertion. They based this divergence on: The different definition of glycaemic index, they do not take into account the fiber contribution, and the different glycaemic response to the same food in different individuals. They consider that cannot be determinate that the observed effect is exclusively due to the food's glycaemic load[30] (Table 3).

Fiber: Dietary fiber intake, especially the fiber that provide the natural resources, has shown that improve the control of cardiovascular risk factors, and improved the glycaemic control, turning into a lower risk of cardiovascular mortality in people with diabetes[27,31]. However, some studies have shown that the effect on diabetes has a modest significance and it is achieved with high amounts of fiber a day but this is far away from a real consumption in daily life (greater than 50 g/d)[32].

Generally, and taking into account the modest beneficial effects on cardiovascular risk factors, in diabetic patients is suggested a consumption of fiber and whole grains at least similar to that recommended for the general population; about 25 g/d for women, and 38 g/d for men or 14 g per 1000 kcal[28].

Sucrose and fructose: Contrary to what one might

think sucrose intakes of 10%-35% of total energy do not have a negative effect on glycaemic or lipid responses when sucrose is substituted for isocaloric amounts of starch[33]. Consume free fructose (naturally occurring from foods such as fruit) did not get worsen the glycaemic control more than other forms of sugar, although it should avoid further intake of 12% of daily calories[28]. Restriction is advised of these sugars in the diet to avoid excessive caloric intake that can contribute to weight gain if are taken in large quantities. Moreover, sugary drinks contain large amounts of fast absorbing carbohydrates and have demonstrated a cardiovascular risk and diabetes increase in the healthy population that consumes them. Especially harmful when are sweetened with fructose free. Although there are not many studies in diabetic patients, there is no reason to think they will not have the same consequences. Therefore, the consumption of these drinks is contraindicated[34].

Non caloric sweeteners: Opposite of natural simple sugars there are sweeteners with lower calorific value. Most are artificial. They do not have caloric contribution, except aspartame (containing 4 kcal/g), and do not increase blood glucose. These sweeteners can be used by diabetic patients. If they are employed to replace glucose, bring the benefit of reducing the kilocalories in the diet[35].

Proteins: It is interesting to make a differentiation between diabetic patients with and without kidney disease. In people without kidney disease, protein intake usually recommended is between 15%-20%; however, reviewing scientific studies no firm conclusion could be reached with respect to this issue. In the literature we can find different randomized clinical trials faced on this issue results. On the one hand there are studies that demonstrate that if 28%-40% of the energy of the diet is taken as proteins there is an improvement of the HbA1c, triglycerides, total cholesterol and/or LDL cholesterol[36], while others studies have not shown a benefit in any of these aspects[37]. In patients with kidney disease, whether if we refer to micro or macroalbuminuria, reducing protein intake below the usual has been undergone various tests and meta-analysis and the evidence has not shown that improve glycaemic control, cardiovascular risk factors or renal disease progression following low-protein diets[27]. With regard to the origin of proteins, there is no difference between animal and vegetable origin in relation to proteinuria[28].

Finally, the proteins in patients with T2DM, although they do not have effect on blood glucose control itself, seems to increase the insulin response so it is not advisable to use proteins in situations of hypoglycaemia.

Fat: Epidemiological studies have related fats with the risk of developing obesity and cardiovascular risk[38]. As in the rest of immediate principles there is no optimal fat proportion and, as a general rule, the recommendations for the general population (between 20%-35%) are applied for diabetic patient, paying special attention if the patient is overweight, then the percentage should be at the lower limits. Despite these recommendations, diabetic patients often take more fat than the recommended[39].

We can distinguish between saturated and unsaturated fats (monounsaturated and polyunsaturated). In addition, has to be specified that trans fatty acids may be a type of unsaturated fat but with harmful effects on the body for its different structure. Distinguish between these types is important because it has been demonstrated that the quality is more relevant than the amount of fat consumed.

There are few studies in diabetic patients about consumption of saturated fatty acids or cholesterol; in this regard the recommendations for patients with diabetes are the same as for the general population: A contribution of saturated fat < 10%, with a minimum intake of trans fatty acids and with a contribution of cholesterol < 300 mg/dL[10] preferably choosing monounsaturated and polyunsaturated fatty acids (including omega-3 fatty acids). Some studies, that have studied the Mediterranean dietary pattern, have demonstrated that monounsaturated fatty acids can improve cardiovascular risk factors and glycaemic control[40], especially if they are replaced with saturated fatty acids.

Omega-3 fatty acids: Although there are unlike results, in general we cannot say that omega-3 supplements have shown clear cardiovascular benefit[41]. However, consumption of products high in omega-3 can be positive in preventing cardiovascular disease[42].

Alcohol: Alcohol should be drunk in moderation and it should not exceed one serving per day for women, or two servings per day in the case of men. To avoid excess of energy when they are consumed, this contribution must be exchanged for other products. This moderate consumption does not harm the glycaemic control but rather in some studies has been found the contrary, with moderation can improve glycaemic control and reduce cardiovascular events.

Despite the above facts, it is very important to note that alcoholic beverages may contribute to the appearance of late hypoglycaemia especially in patients in treatment with hypoglycaemic drugs, so we should warn the patient to pay attention to any symptoms of hypoglycaemia[28].

Sodium: The recommendation for the general population to reduce sodium intake to less than 2300 mg/d shall also apply to patients with diabetes mellitus. When these also have hypertension, which is very common, reduced sodium intake should be individualized[43].

Specific supplements: The potential benefits of

Table 4 Relationship between maximum oxygen consumption, % of maximum heart rate and subjective perceived exertion

Intensity	% oxygen consumption	% maximum heart rate[1]	Subjective perceived exertion
Very light	< 20	< 35	< 10
Light	20-39	35-54	10-11
Moderate	40-59	55-69	12-13
High	60-84	70-89	14-16
Very high	> 85	> 90	17-19
Maximum	100	100	20

[1]Maximum heart rate = 220-age. Available from: URL: American Diabetes Association. Physical Activity/Exercise and Diabetes. *Diabetes Care* 2004; **27** (Suppl 1): S58-S62.

dietary supplements for diabetic patients with various specific nutrients have been subjected to trials. In despite of this, reliable data has not been observed to confirm benefits in glycaemic control supplementing because of supplement the diet with antioxidants as vitamin and carotenes, micronutrients such as chromium or other herbs. The recommendations of vitamins and minerals are not different from the general population, they are provided by a varied diet[38].

Exercise

The physical activity and exercise are one of the basic strategies in the treatment of diabetes. Promoting exercise, within a specific plan, provides in general terms multiple benefits: Increased insulin sensitivity in tissues, improvement of glycaemic control[44], benefits in lipid profile and blood pressure, maintenance or weight loss, cardiovascular benefits, better quality of life, psychological well-being and improvement of depression[10].

Benefits of glycaemic control: In some studies it has observed a significant decrease in HbA1c in patients with T2DM who do exercise. The difference in the degree of improvement observed in the different studies will depend on the characteristics of the patient and the type of training, thus, it is more effective when training programs are based on aerobic exercises of programs based on muscle strength in isolation[45].

Other benefits: The physical exercise also brings improvement in other metabolic parameters. It helps control cardiovascular risk factors (dyslipidaemia, hypertension, weight maintenance, psychological benefits, reduces mortality, improvement cardiorespiratory fitness and peripheral neuropathy[10,45].

Types of exercise: Both aerobic and resistance exercises have demonstrated benefits in people with diabetes through increased glucose uptake and decreased insulin resistance.

Though aerobic exercise in isolation seems to get better benefits that resistance exercise[45], in patients with diabetes is recommended the combination of both types because the effect is greater than if each one is performed in isolation[46,47].

This type of training has been traditionally recommended for patients with T2DM. A frequency of at least 3 d per week is recommended, preferably if it can be increased to 5 d with no more than two consecutive days between periods of activity, because the increase of the sensitivity and the glucose tolerance is maintained for about 12-24 h. It should be done with moderate intensity which is 40%-60% of maximum aerobic capacity. This corresponds to 55%-69% of maximum heart rate according to age (maximum heart rate = 220-age)[47]. Another method for measuring the intensity can be the subjective perception of the effort that assigns values to 20 points according to the patient judgment about the activity performed (Table 4). A moderate-intensity exercise can also be an activity that can be conducted while maintaining an uninterrupted conversation.

The effect of exercise in T2DM is clearly related to the volume done, thus, in different societies, it is recommended at least a minimum of 150 min per week[43,47]. Despite following the same recommendations, it has recently published a review where it is expounded that shorter performance exercises, with reference to the accumulated time during the week, keeps some benefit although this is less[48].

This type of exercise should be performed 2-3 times a week on non-consecutive days. For optimal gains in strength and insulin action, training should be moderate (50% of 1 repetition maximum) or vigorous (75%-80% of 1 repetition maximum). Each session should include from 5 to 10 exercises involving the use of large muscle groups. Ten to fifteen repetitions of each exercise (30-45 s) have to be made. Between each series should be left between 1-2 min for the recovery. Supervision by a professional can ensure an appropriate enforcement and progression of the exercise that optimized the benefits and reduce the risk of complications[47].

Although they have not demonstrated benefits in glycaemic control, these exercises are also recommended and can be very useful in older patients with T2DM[49].

Unstructured physical activity: It is also recommended to advise patients to increase energy expenditure in activities of daily life. It requires an increase of unstructured physical activity (walking more in the day, climb the stairs...)[50].

Prescription of a specific plan: Exercise should be prescribed individually for each patient and taking into accounts the characteristics of the person. Initially, the guidelines should recommend a slow progression and, if it is necessary, the patient has to start with low volumes of work. Recommendations should take into account the type of diabetes and the treatment utilized, the possibility that patients have diabetic foot, retinopathy, neuropathy, nephropathy or some

degree of cardiovascular risk[49]. Training plans that are supervised by professionals have proved to be more effective as this study have demonstrated. In it, is compared a supervised program against a general advice, and although in both an increase in physical activity is observed, some better effects in HbA1c and cardiovascular risk factors in the supervised group have been seen[51].

Before starting the exercise would be advisable to pre-clinical evaluation, paying special attention to physical ability, complications of diabetes and comorbidities that constrain the realization of physical activity. For patients at high cardiovascular risk or for those who start high-intensity exercises, the ADA recommends performing an effort test with a grade of recommendation C[47].

Exercise and diabetes complications: The presence of diabetes complications involves a number of considerations at the time of writing prescriptions of physical exercise in these patients.

The physical exercise has proved benefits in reducing the appearance of peripheral neuropathy[52]. When it is already present, it is recommended to avoid exercises that cause impacts of repetition in the lower extremities and especially in patients with foot ulcers and wounds[53]. Furthermore, recent studies have demonstrated that moderate intensity walking do not increase the risk of ulcers.

In respect of the weight-bearing exercises, it can be performed while there are no ulcers or foot lesions. In any case it should pay attention and examine the feet and always wear suitable shoes.

The presence of retinopathy advises against the practice of physical activities that increase intrathoracic pressure (Valsalva manoeuvre), or high-intensity exercises by the risk of retinal detachment or intravitreal haemorrhage. The exercises with low and moderate intensity (walking, swimming...) are perfectly authorized and they can be done safely. Contact exercises like boxing should be avoided because of the risk of impact[50].

Exercise for diabetic patients is beneficial at any stage of renal function. In epidemiological studies it has been shown to improve renal function. Promotes muscle strengthening in case of kidney failure that helps to counteract sarcopenia, and improves various parameters in patients on dialysis, so with supervision and restraint exercise is recommended and although they have been transient increases in microalbuminuria with sessions of exercise (because of increasing blood pressure) is not considered as a marker of persistent microalbuminuria[50].

Physical activity has many beneficial cardiovascular effects but must take into account some considerations when there is vascular disease. Patients with diabetes that present a moderate or high cardiovascular risk should be included in supervised cardiac rehabilitation programs, because exist an association with mortality. In addition, during the exercise there is an increased activity of the sympathetic nervous system and catecholamines and decrease vagal tone[47,50].

In people with peripheral arterial disease benefits from the practice of sports aerobics and resistance also exist because of the improvement of the mobility, functional capacity, pain tolerance and quality of life[47].

Moderate physical exercise can improve the autonomic nervous system both in patients with autonomic neuropathy and those who do not have it[54], however it may represent a prescription limitation because it may favour silent ischemia, doubling mortality, impairing exercise tolerance and decreasing the maximum heart rate and thus a prior cardiovascular study is recommended[55].

Exercise with uncontrolled blood sugar

Hyperglycaemia: In T2DM is very strange developing a true insulin deficiency, as in type 1 diabetic, so if the patient feels well is not necessary to postpone the exercise by hyperglycaemia, although they must ensure an adequate hydration state[56].

In non-diabetic person with aerobic exercise the increase of the glucose uptake is offset with similar increase of the hepatic glucose, but in diabetic person the muscle uptake is greater than the liver's production although the risk of hypoglycaemia is minimal if hypoglycaemic drugs are not taken[47]. However, if in addition to the effect of exercise add up the effects of hypoglycaemic drugs, we recommend a series of precautions mainly based on carbohydrate intake and adjust drug doses. If the levels before exercise are less than 100 mg/dL should take a supplement of 15 g of carbohydrates before exercise. This measure should only be recommended if blood glucose lowering drugs (secretagogues or insulin) are taken. If the control is with other drugs, supplements are not required if the exercise is less than an hour[56]. It is important to note that regardless of the initial levels, if the exercise is prolonged a monitoring could be required and also intakes over the same period.

Before physical activity, to prevent the appearance of hypoglycaemia during exercise, doses of drugs such as insulin secretagogues or insulin (especially the latter) can be decreased. These measures can be associated with dietary measures mentioned above. During the hours after exercise glucose needs increase, so after exercise delayed hypoglycaemia can happens. This hypoglycaemia should be expected and may require reducing the dose of drugs after exercise and/or increase the intake after it[47].

ORAL AGENTS

Metformin

Metformin is considered the agent of first line for treatment of T2DM, in the absence of contraindications[6,13,57].

Mechanism of action[58]: Metformin can change

the composition of gut microbiota[59] and activate mucosal AMP-activated protein-kinase (AMPK) that maintain the integrity of the intestinal barrier. These effects, in combination with the activation of AMPK[60] in hepatocytes appear to be the mechanism by which metformin decrease lipopolysaccharide (LPS) levels in circulation and in the liver.

After being delivered to the liver from the intestines, metformin can inhibit gluconeogenesis through four different mechanisms[61]: (1) by activating hepatic AMPK through liver-kinase B1 and decreased energy charge (9, 10); (2) through the inhibition of glucagon-induced cAMP production by blocking adenylcyclase (11); (3) in high concentrations (5 mmol/L) inhibit NADH coenzyme Q oxidoreductase (complex I) in the mitochondrial electron transport chain (12) to reduce ATP levels and increase AMP/ATP ratio. This increased ratio should activate AMPK; and (4) the inhibition of mitochondrial glycerol phosphate dehydrogenase (mG3PDH)[58], will affect transport of NADH from the cytoplasm into mitochondrion, suppressing gluconeogenesis process from lactate.

Also, metformin works through the Peutz-Jeghers protein LKB1. LKB1 is a tumour suppressor, and activation of AMPK through LKB1[62] may play a role in inhibiting cell growth.

Indications and contraindications: Metformin is the drug of first-line for many patients with T2DM. It decreases fasting blood glucose by approximately 20% and HbA1c by 1.5%. It can be given in combination with sulfonylureas, glinides, alpha-glucosidase inhibitors, insulin, thiazolidinediones (TZD), glucagon-like peptide-1 receptor agonist (RA-GLP1), dipeptidylpeptidase 4 inhibitors (iDPP4), and sodium-glucose co-transporter 2 inhibitors (iSGLT2). Metformin is contraindicated in patients with factors that predispose to lactic acidosis. The predisposing factors are: A renal function damaged, concomitant liver disease or excessive alcohol intake, unstable or acute heart failure and personal history of lactic acidosis.

The precise serum creatinine and estimated glomerular filtration rate (eGFR) limits for the use of metformin remain uncertain. In the metformin prescribing information is contraindicated when creatinine level is above 1.4 mg/dL in woman and 1.5 mg/dL in men, and with eGFR < 60 mL/min. However, in observational studies of T2DM patients and eGFR 45-60 mL/min, improved clinical outcomes have been reported. Nowadays[63-65], in patients with eGFR above 45 mL/min, metformin can be utilized. The absolute contraindication is with GFR < 30 mL/min. With eGFR 30-45 mL/min, in clinical practice, currently we reduce metformin dose by a half. It is very important to advise patients with eGFR 30-60 mL/min to stop taking metformin if they develop any condition associated with dehydration, sepsis or hypoxemia. Also metformin should be stopped prior to intravenous iodinated contrast.

Side effects: The most frequents are gastrointestinal, such as anorexia, nausea, abdominal discomfort and diarrhoea; they are usually mild and transient. Also, metformin reduces intestinal absorption of vitamin B12.

Less common is lactic acidosis. In a review[66] of 347 randomized trials and prospective cohort studies, there were no cases of lactic acidosis. However, is very important because of the high case-fatality rate. Predisposing factors are all situations that predispose to hypoperfusion and hypoxemia (sepsis, heart failure, dehydration, acute or progressive renal impairment).

Cardiovascular effects: Metformin does not have adverse cardiovascular effects, and it appears to decrease cardiovascular events as we saw in UKPDS, and during the post-interventional observation period of the UKPDS, in which reductions in the risk of macrovascular complications were maintained in the metformin group.

Metformin also has a lipid-lowering activity, and it result in a decrease in free fatty acid concentration, serum triglyceride, small decrease in LDL cholesterol and a modest increase in HDL cholesterol.

Cancer incidence: Observational data suggest that metformin decreases cancer incidence[67,68]. In different meta-analyses in T2DM patients, use of metformin compared with non-use or with use of other diabetes treatment, was related with a reduced risk of all cancers and lower cancer mortality[69,70]. The majority of the trials were not designed to explore cancer outcomes, so we must be prudent in the interpretation of their results.

Insulin secretagogues: Sulfonylureas and meglitinides

Sulfonylureas and meglitinides or glinides (insulin secretagogues) are two different classes of oral hypoglycaemic drugs but they have a common mechanism of action, and both stimulate pancreatic beta cells to release insulin.

Sulfonylureas are a classic first or second-line therapy for patients with T2DM[71], and since their introduction to clinical practice in the 1950s they have been widely utilized[72]. They are utilized as a reference to compare the efficacy and safety of other hypoglycaemic drugs excluding insulin.

Meglitinides stimulate insulin release through similar mechanisms but they have a different subunit binding site, with a more rapid absorption and more rapid stimulus to insulin secretion. However they require more frequent dosing[73].

Mechanism of action: Both sulfonylureas and glinides base their mechanism of action in increasing insulin secretion, which is regulated by ATP-sensitive potassium channels (KATP potassium channel) located in the membrane of pancreatic beta cells[74]. Although the receptor's binding site is different for sulfonylureas

and glinides, they both induce channel closure and cell depolarization leading to an increase in cytoplasmic calcium level and consequently insulin secretion[37].

Pharmacokinetics: Differences in pharmacokinetic and binding properties of insulin secretagogues result in the specific responses that each drug produces. Sulfonylureas can be divided into first- and second-generation agents. Glyburide (known as glibenclamide in Europe), glipizide, gliclazide and glimepiride are second-generation sulfonylureas[57]. New generation agents are more potent and have fewer adverse effects[37]. Although second-generation sulfonylureas are equally effective, there are differences in absorption, metabolism, and duration of action as well as in effective dose; for example, glyburide has active metabolites that can prolong his action.

There are two different glinides: Repaglinide and nateglinide. Repaglinide is a member of the meglitinide family different from the sulfonylurea. Nateglinide is a derivate of phenylalanine and it is structurally difference from sulfonylureas and meglitinide. They both cause less hypoglycaemia and less weight gain due to their shorter half-life and a different sulfonylureas receptor binding site, leading to faster absorption and a more rapid stimulus to insulin secretion[37].

As a result of their pharmacokinetics, the major effect of sulfonylureas is the reduction of fasting plasma glucose concentrations, whereas meglitinides mainly reduce postprandial glucose[75].

Advantages and effectiveness: Sulfonylureas and meglitinides can be effective when employed as monotherapy, or in combination with other oral hypoglycaemic drugs or insulin. Sulfonylureas are the most cost-effective glucose-lowering agents, have been on the market for a long time[37], and are widely utilized because of their long term efficacy and safety history, low cost and extensive clinical trial data demonstrating good glucose-lowering efficacy[76,77]. The glucose-lowering effectiveness is said to be high for sulfonylureas (expected HbA1c reduction 1.0%-1.5%) and generally lower for meglitinides (0.5%-1.0%)[9,57].

In the Consensus of ADA/EASD 2015 sulfonylureas and glinides appear as an alternative to metformin when metformin is contraindicated or not tolerated, and they represent an alternate treatment option in double and triple therapy[57], whereas in the Consensus of the American Association of Clinical Endocrinologist (AACE) 2016, sulfonylureas and glinides appear as the last alternative both in monotherapy and combined treatment[9].

Side effects: Loss of efficacy, hypoglycaemia and weight gain represent the main problems related to the use of these drugs.

Over time insulin secretagogues lose effectiveness (secondary failure), caused by an exacerbation of islet dysfunction with beta cell failure[78,79]. As a result, the percentage of patients maintaining adequate glycaemic control decreases progressively. Although this effect may also be related to disease progression, it has shown an increase in secondary failure than other agents[80].

Weight gain can be *via* many of the same mechanisms that are triggered by insulin therapy, and it has been observed in different studies[81,82]. However, metformin might counter the weight gain effect when used in combination[81,83]. Different generations of sulfonylureas have shown to cause weight gain and its magnitude appears to correlate with the propensity to cause hypoglycaemia. It may also occur with meglitinides as they have similar profiles[76], but it seems to occur in a lesser extent due to their short action[78].

Hypoglycaemia is the most common adverse effect[83,84], especially with long-acting sulfonylureas (such as glyburide/glimepiride)[85]. New generation sulfonylureas have shown to have a significantly lower risk of hypoglycaemia. Meglitinides generally have less risk of hypoglycaemia[37], thus being useful for individuals in whom the goal of avoiding hypoglycaemic events is important.

The risk factors for hypoglycaemia are inconsistent eating patterns in older individuals (meglitinides can be useful in these patients), malnutrition, alcohol ingestion, renal insufficiency, hepatic failure, hypothyroidism or drug interactions[86,87]. The risk of hypoglycaemia, as well as considerations of the risk-to benefit-relationship, is particularly relevant in older individuals where results from trials have suggested that aggressive control may not have significant benefits and may present some risk[6].

Cardiovascular disease: Sulfonylureas have been associated with increased cardiovascular risk, especially when it comes to glyburide/glibenclamide. Some studies[88,89] support this association, which can be explained by the interference with ischemic preconditioning, a protective autoregulatory mechanism in the heart. However, other studies like UKPDS, ADVANCE and ACCORD and many meta-analyses failed to proof an increased risk in cardiovascular mortality or morbidity[76]. Therefore, it remains unclear whether sulfonylureas are associated with an increased cardiovascular risk but as glibenclamide may indeed be when compared with other sulfonylureas, clinicians should consider possible differences in risk of mortality if a sulfonylurea is to be utilized.

Other considerations: Most insulin secretagogues undergo significant renal clearance except for meglitinides, and the risk of hypoglycaemia is higher in patients who have chronic kidney disease (CKD) especially with glyburide/glibenclamide which has a prolonged duration of action and active metabolites[58]. In patients with liver disease, sulfonylurea is not specifically contraindicated and meglitinides can also be employed. When liver disease is severe, insulin

secretagogues have an increased risk of hypoglycaemia and should be avoided[57,90].

Sulfonylureas have several drug-drug interactions as they are metabolized by cytochrome p450[84]. Repaglinide with gemfibrozil is contraindicated because of its higher risk of hypoglycaemia.

Alpha-glucosidase inhibitors

There are three currently available agents, acarbose, miglitol and voglibose[37]. Their properties are different from other antidiabetics owing to its unique mode of action. Acarbose has been used for over 20 years in the treatment of hyperglycaemia[91].

The alpha-glucosidase inhibitors reduce postprandial triglycerides but their effect on LDL and HDL cholesterol levels and fasting triglycerides is insignificant and inconsistent[75,92]. Alpha-glucosidase inhibitors rarely induce hypoglycaemia, because these agents do not stimulate insulin release, and do not significantly affect body weight[82].

Acarbose has demonstrated to have beneficial effects by reducing the risk of cardiovascular disease and slowing the progression to diabetes in patients with impaired glucose tolerance[93,94].

Mechanism of action: Alpha-glucosidases are enzyme complexes located in the brush border membrane of the small intestine and hydrolyse oligosaccharides into monosaccharides[95]. Alpha-glucosidases inhibitors are structurally similar to natural oligosaccharides with higher affinity for alpha-glucosidases[91], and they produce a reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. This cause delayed carbohydrate absorption and digestion, and results in a reduction in postprandial hyperglycaemia. The undigested carbohydrates in the lower parts of the small intestine increase plasma RA-GLP1 levels[95]. Because reduced blood glucose concentrations, alpha-glucosidase inhibitors do not enhance insulin secretion[91,95].

Efficacy: In general, alpha-glucosidase inhibitors have modest HbA1c lowering effects. In the Consensus of ADA/EASD 2015, alpha-glucosidase inhibitors are not included in the algorithm due to their lower efficacy and limiting side effects compared to other options[57], whereas in the Consensus of AACE 2016, alpha-glucosidase inhibitors appear only before sulfonylureas and glinides as monotherapy and combined treatment[9].

Side effects: The side effects are mainly gastrointestinal and include flatulence, diarrhoea and abdominal pain. These symptoms are usually mild, but they may reduce compliance and they are the most common reason for discontinuation treatment[94,95]. These symptoms occur when undigested carbohydrates arrive to the colon and as a result, there is a fermentation by bacteria in the large bowel and intestinal gas production[91]. For this reason, they are contraindicated in patients with chronic intestinal disorders associated with impaired digestion or absorption, and with conditions that may worsen when an intestinal gas increase appears (hernias, intestinal obstruction and intestinal ulcers). Treatment should be discontinued immediately if there is or is suspected ileus or sub ileus. To maximize the potential for these agents to be well tolerated, start with a low dose and increase slowly[37].

Alpha-glucosidase inhibitors are not recommended for patients with creatinine clearance < 25 mL/min and they can produce asymptomatic elevation of liver enzymes, for this it is necessary a control of liver enzymes[96]. In hypoglycaemia (when it is associated with sulfonylureas, glinides and insulin), like inhibitors of α-glucosidase delay absorption and digestion of sucrose, patients must take glucose.

Thiazolidinediones

Two TZD are currently available in United States: Rosiglitazone and pioglitazone. In Europe, since 2010, rosiglitazone was suspended by the European Medicines Agency, based on the overall risks of rosiglitazone exceed their benefits. French and Germany Medicines Agencies also discontinued pioglitazone in 2011.

Mechanism of action: TZD increase insulin sensitivity by acting on muscle, adipose tissue and liver to increase glucose utilization and decrease glucose production. TZD bind to peroxisome proliferator-activated receptors (PPARs). PPAR-γ is found predominantly in central nervous system, macrophages, vascular endothelium, adipose tissue and pancreatic beta-cells. The concentration of PPAR gamma is increased in the skeletal muscle of obese and diabetic patients[97]. In the central nervous system PPAR-gamma activation mediates weight gain by stimulating increased feeding[98]; this is, in part, the reason for weight gain associated with TZD.

PPAR-alpha is found predominantly in liver, skeletal muscle, heart and vascular walls. Rosiglitazone is purely PPAR-gamma agonist, while pioglitazone has also some PPAR-alpha effects; therefore they have different effects on lipids. Pioglitazone produces a more favourable lipid profile: LDL-cholesterol remained constant during treatment while rosiglitazone raises them; in addition decreased more triglyceride levels than rosiglitazone. HDL-cholesterol increased more or less 10% with both of them.

TZD also may improve blood glucose levels by preserving pancreatic beta-cell function. They are probably similar in efficacy to metformin in monotherapy but we don't usually choose them because of their adverse effects and cost. Also, they are effective in combination therapy, but again, we typically prefer combination with other drugs with less adverse effects. TZD should not be given to diabetic patients with a history of heart failure or low bone mass.

The ratio between benefit and risk at cardiovascular system of rosiglitazone and pioglitazone remains unclear. Meta-analyses and observational studies (RECORD study, BARI 2D, PROactive trial) suggest caution with

rosiglitazone use and also with pioglitazone.

Side effects

Weight gain: The weight gain is the result of diverse mechanisms as: Fluid retention, the activation of PPAR-γ in the central nervous system (which increases feeding) and the up regulation of genes that facilitate adipocyte lipid storage (in part weight gain may be also a result from the proliferation of new adipocytes[99]). It's time and dose dependent.

Heart failure: PPAR-γ is more abundant in the collecting tubules of the nephron; the PPAR-gamma stimulation (induced by TZD treatment) activate sodium reabsorption in the luminal membrane of the collecting tubule cells[100], leading to a fluid retention that may lead to the precipitation of heart failure or worsening it. Peripheral oedema occurs in 4%-6% of patients in treatment with TZD, and this percentage is higher in patients with heart failure history. Because of the risk of heart failure the American Heart Association and the ADA published a consensus statement in 2003[101].

Because of their mechanism of action (they improve blood glucose by increasing insulin sensitivity) TZD monotherapy cause hypoglycaemia less frequently than sulfonylureas or insulin.

In preclinical studies pioglitazone increased bladder tumours in rats. Latter the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) saws more cases of bladder cancer: 14 *vs* 5, in the treatment group[102]. In an analysis of an ongoing 10-years observational study, there wasn't a significant association between pioglitazone and cancer[103], but the risk of bladder cancer was significantly increased in those with the longest exposure and highest cumulative dose. Using data from the Adverse Even Reporting System of the United States FDA, again risk of bladder cancer was higher with pioglitazone[104]. Because of these in 2011 German and French Medicines Agencies suspended the use of pioglitazone.

Decrease bone density and increase fracture risk. The activation of PPAR-gamma has been demonstrated to down regulate components of the IGF-1 system, and IGF-1 is an important regulator of osteoblast proliferation and differentiation[105]. The absolute increase in risk fracture seems to be small and occurred with both of them, rosiglitazone and pioglitazone; the fractures are more frequently in the distal upper or lower extremities. These treatments should not be utilized in women with low bone density or with risk factors for fracture.

Troglitazone suspended its commercialization due of severe hepatocellular injury[106]. FDA currently recommends periodic monitoring of liver function in patients in treatment with rosiglitazone or pioglitazone.

Dipeptidyl peptidase-4 inhibitors

The incretin agents (GLP1 and GIP), secreted by intestine L cells, increase insulin secretion and inhibit glucagon in response to nutrient inputs. The glucoregulatory effects of incretins are the basis for treatment with inhibitors of DPP4 in patients with T2DM. Agents that inhibit DPP4, an enzyme that rapidly inactivates incretins, increase active levels of these hormones and, in doing so, improve islet function and glycaemic control in T2DM.

iDPP4 are used as monotherapy in patients inadequately controlled by diet and exercise, and dual therapy in combination with metformin, TZDs and insulin. iDPP4 are well tolerated; they have a low risk of producing hypoglycaemia, and maintain the patient's weight. We have five iDPP: Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin and Alogliptin.

Sitagliptin: Sitagliptin, which is approved for the treatment of T2DM in many countries, can be employed alone or dual therapy with sulfonylurea, metformin or TZD or third therapy. The normal dose of sitagliptin is 100 mg once daily; half dose is utilized in patients with an eGFR 30-50 mL/min, and quarter dose in those with an eGFR < 30 mL/min[107].

Monotherapy with this drug there are multiple studies, with significant reduction in HbA1c. The results of a study with sitagliptin monotherapy for 18 wk were: HbA1c significantly decreased with sitagliptin 100 and 200 mg compared to placebo (low HbA1c *vs* placebo: -0.48% and -0.60% respectively). Sitagliptin also significantly reduced fasting blood glucose *vs* placebo. Patients with baseline HbA1c higher (> or = 9%) had greater reductions in HbA1c subtracted sitagliptin placebo (-1.20% for 100 mg and -1.04% in the case of 200 mg) than those with HbA1c < 8% (-0.44% and -0.33%, respectively) or > or = 8% to 8.9% (-0.61% and -0.39%, respectively). Sitagliptin had a neutral effect on body weight[108].

In dual therapy studies the results confirm that sitagliptin was as effective as glipizide in patients inadequately controlled with metformin. In one of them the following results were found a year: From a mean baseline of 7.5%, HbA1c changes from baseline were -0.67% at week 52 in both groups, confirming non-inferiority. The proportions achieving an HbA1c < 7% were 63% (sitagliptin) and 59% (glipizide). Fasting plasma glucose changes from baseline were -0.56 mmol/L (-10.0 mg/dL) and -0.42 mmol/L (-7.5 mg/dL) for sitagliptin and glipizide, respectively[109]. With sitagliptin were observed less hypoglycaemia and less weight gain than with glipizide.

Vildagliptin: This is an iDPP4 which FDA was not approved so that is not being used in the United States. The usual dose is 50 mg twice daily when utilized as monotherapy, with metformin, or with a TZD, and 50 mg once daily (in the morning) when utilized with a sulfonylurea. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance ⩾ 50 mL/min). In patients with moderate or severe renal impairment, the dose is 50 mg once daily.

In some studies comparing the efficacy and safety of vildagliptin compared with placebo target the treatment difference (vildagliptin-placebo) in adjusted mean change (AM Delta) ± SE in HbA1c from baseline to endpoint it was -0.7% ± 0.1% ($P < 0.001$) and -1.1% ± 0.1% ($P < 0.001$) in patients receiving 50 or 100 mg of vildagliptin, respectively. The difference between treatments in the Delta GPA (GPA) was -0.8 ± 0.3 mmol/L ($P = 0.003$) and -1.7 ± 0.3 mmol/L ($P < 0.001$) in patients receiving 50 or 100 mg of vildagliptin, respectively[110].

Saxagliptin: Saxagliptin is approved as a drug for home treatment of T2DM or dual therapy for patients not controlled with a sulfonylurea, metformin or TZD. The dose is 2.5 or 5 mg of saxagliptin once daily. The dose of 2.5 mg is recommended for patients with an eGFR ⩽ 50 mL/min and patients taking drugs inhibitors of cytochrome P450 3A4/5 (*e.g.*, ketoconazole), Saxagliptin monotherapy is effective, achieving reductions in HbA1c of 0.5 in naive patients *vs* placebo[111,112]. There are studies with saxagliptin (2.5, 5 and 10 mg) in dual therapy with metformin showed a statistically significant adjusted mean HbA1c decrease from baseline to week 24 compared to placebo (-0.59%, -0.69%, and -0.58% *vs* +0.13%; all $P < 0.0001$)[113]. There are also studies showing the efficacy of sitagliptin in combination with sulfonylureas and TZD.

Linagliptin: The dose of linagliptin is 5 mg once daily. It is eliminated mainly through the enterohepatic system so it is not necessary to adjust the dose in patients with renal or hepatic impairment. Inducers of CYP3A4 or P-glycoprotein (*e.g.*, rifampicin) may reduce the effectiveness of this agent. In patients receiving these drugs should avoid the use of linagliptin.

In a monotherapy study *vs* placebo, linagliptin achieved a reduction in HbA1c of 0.44% against rising 0.25% with placebo in 6 mo[114]. In a 24 wk study in triple therapy in patients treated with metformin and sulfonylureas that was added linagliptin or placebo, appeared a reduction in HbA1c of 0.72% in the group with linagliptin *vs* 0.1% in the group with placebo[115].

Alogliptin: The usual dose of alogliptin is 25 mg once daily, with dose reductions to 12.5 mg once daily in patients with creatinine clearance between 30 and 60 mL/min and to 6.25 mg daily in patients with creatinine clearance < 30 mL/min or undergoing dialysis[116].

In a study to twelve weeks in patients treated with metformin with poor control of their diabetes, alogliptin group achieved a reduction in HbA1c of 0.64% compared to an increase of 0.22% in the placebo group[117]. In another 26 wk studies, with alogliptin (12.5 or 25 mg once a day) *vs* placebo in patients with poorly controlled T2DM on a stable dose of glyburide ($n = 500$) or insulin (alone or in combination with metformin, $n = 390$) there were greater reductions in HbA1c in the alogliptin groups (mean change in HbA1c from baseline -0.39, -0.53 and +0.01 percentage points for the 12.5, 25 mg, and placebo groups, respectively, in the glyburide trial, and -0.63, -0.71 and -0.13 percentage points, respectively, in the insulin trial)[118,119].

Side effects: These drugs are considered very safe since both the risk of hypoglycaemia and other adverse effects are rare. All of them at increased risk of hypoglycaemia in combination with sulfonylureas or insulin. In comparative studies have not observed any significant differences between them in the risk of hypoglycaemia. With vildagliptin and alogliptin have been reported cases of hepatic dysfunction unusually still advisable to monitor liver enzymes during the first three months of treatment. If an increase in transaminases of three times the upper limit of normal or greater persists, the drugs should be discontinued.

At present, there is insufficient data to know whether there is a causal relationship between acute pancreatitis and iDPP4[120-123]. They should be discontinued in patients with persistent severe abdominal pain. In patients with pancreatitis should not start these drugs, or if there is a history of this disease.

Commonly reported side effects include headache, nasopharyngitis, and upper respiratory tract infection[124,125]. Some, but not all, studies have reported a slight increased risk of gastrointestinal side effects with sitagliptin[108,109,126].

Cardiovascular effects: Sitagliptin, saxagliptin and alogliptin have been studied for cardiovascular safety. They are TECOS, SAVOR-TIMI and EXAMINE studies respectively, with thousands of patients at high cardiovascular risk with a median follow up of 18 to 36 m.

In the TECOS study with sitagliptin 14735 patients with T2DM and established cardiovascular disease (history of major diseases of the coronary artery, ischemic cerebrovascular disease or peripheral arterial atherosclerotic disease) were randomized a group with sitagliptin and one with placebo, plus other diabetes medications (mainly metformin, sulfonylurea, insulin)[127]. After three years, the primary cardiovascular combined outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) was observed in a similar proportion of diabetics (11.4% and 11.6% in the sitagliptin and placebo group's human resources, respectively, 0.98; 95%CI: 0.89-1.08). There was no significant difference in any of the individual components of the composite endpoint or the rate of hospitalization for heart failure (3.1% in each group).

In the test with saxagliptin (SAVOR-TIMI), 16492 patients with T2DM and either a history of cardiovascular disease or multiple risk factors for vascular disease were randomized to the branch of saxagliptin or placebo, and other medicines for diabetes (such as metformin, sulfonylureas, insulin). After a two-year follow-up, the first target (combination of cardiovascular death, nonfatal ischemic stroke or nonfatal myocardial

infarction) appeared in a similar number of diabetics in proportion, 7.3% and 7.2% in the saxagliptin and placebo, respectively; hazard ratio (HR) 1.00, 95%CI: 0.89-1.12[128]. Significantly more patients in the field of saxagliptin were hospitalized for heart failure (3.5% *vs* 2.8%; HR = 1.27, 95%CI: 1.07-1.51). It stresses significantly the hospitalization for heart failure in the saxagliptin study[129] increase. However, the possible association between heart failure and iDPP4 has been linked to other epidemiological data and claims data[130,131].

In the EXAMINE trial alogliptin, 5380 patients with T2DM and either an acute myocardial infarction or unstable angina requiring recent hospitalization were randomized to alogliptin or placebo, along with other antidiabetic (mainly metformin, sulfonylureas, insulin)[132]. At 18 mo follow-up, the primary composite endpoint including cardiovascular death, nonfatal stroke, or nonfatal myocardial appeared in a very similar proportion of patients (11.3% and 11.8% in the branches of alogliptin and placebo respectively; HR 0.96, 95% of the unilateral CI: 1.16). In a post hoc analysis of the data, there was no significant difference in the rate of hospitalization for heart failure (3.1% and 2.9% in the branches of alogliptin and placebo, respectively; HR = 1.07, 95%CI: 0.79-1.46)[133].

Sodium glucose co-transporter-2 inhibitor

iSGLT2 inhibit renal reabsorption of glucose, increase its excretion and reduce hyperglycaemia in patients with T2DM. Therefore, reducing the reabsorption of glucose by inhibition of SGLT2 is a new way to treat T2DM. The increase in glucosuria and diuresis produced results in a reduction in weight and blood pressure[134].

Kidneys from healthy people filter approximately 180 g of glucose each day through renal glomerulus and reabsorbed in the then proximal convoluted tubule. This is possible by passive and active co-carriers which are known as glucose transporter (GLUT) and SGLT[135] conveyors. There are two types of SGLT; SGLT1 located mainly in the small intestine and the kidney proximal convoluted tubule, and SGLT2 located only in the proximal tubule (segment 1 and 2), that are responsible for about 90% of glucose reabsorption[7]. The other 10% of the glucose is reabsorbed by SGLT1 in segment 3. SGLT2 inhibitors block the SGLT2 transporter in the proximal tubule, to lower glucose reabsorption and increase its excretion in the urine. Glucose is excreted in the urine and plasma levels are reduced by improving glycaemia figures plasma[136-138]. It is an independent mechanism of insulin, there is low risk for hypoglycaemia, and no risk of fatigue or overstimulation of the beta cells[139]. Due to its mode of action is based on normal glomerular-tubular function; the iSGLT2 efficiency is lower in patients with renal failure[140]. The three most representative drugs family iSGLT2 are: Dapagliflozin, canagliflozin and empagliflozin.

Dapagliflozin: Dapagliflozin was the first iSGLT2 employee, and has many published data from clinical trials. In phase 3 trials comparing placebo for 24 wk and dapagliflozin (2.5, 5 and 10 mg once daily) used alone or added to metformin[141], pioglitazone[142], glimepiride[143] or insulin[144] was observed that HbA1c and fasting plasma glucose in patients with T2DM was reduced. In tests longer-term (102 wk) added to metformin, dapagliflozin resulted in a sustained decrease in HbA1c, glucose fasting blood glucose and weight without increasing the risk of hypoglycaemia in patients with T2DM not controlled on metformin alone[145]. The initial decrease in HbA1c observed at 24 wk with both doses of dapagliflozin (5 or 10 mg) added to metformin was maintained at 102 wk, and was superior to placebo (-0.58%, -0.78% and 0.02% against). Also the low fasting plasma glucose with both doses of dapagliflozin, remained and was higher than placebo (-1.47 mmol/L and -1.36 mmol/L *vs* -0.58 mmol/L). This drug has studies which compared with patients whose hyperglycaemia glipizide was poorly controlled by metformin[146]. After 52 wk, a drop in HbA1c starting from the baseline of -0.52% is target with dapagliflozin (≤ 10 mg/d) and glipizide (≤ 20 mg/d). Weight reduction was greater with dapagliflozin (-3.2 kg) *vs* glipizide (+1.4 kg). Dapagliflozin (≤ 10 mg/d) in T2DM patients was non-inferior to glipizide (≤ 20 mg/d) in reduction of HbA1c at 52 wk (both -0.52%). At 4 years the HbA1c reduction is attenuated in both groups, but more in the glipizide *vs* dapagliflozin (+0.2% *vs* -0.1%). There were differences in weight change, with weight loss in the dapagliflozin group *vs* weight gain in the glipizide group (-3.95 kg *vs* +1.12 kg). In the dapagliflozin group decreases the mean average of systolic blood pressure, but did no change in the glipizide group (difference: -3.7 mmHg)[146].

Canagliflozin: Canagliflozin was the first of this family of drugs approved by the FDA and began its commercialization in March 2013 for use in T2DM. It is an effective drug in monotherapy and after 26 wk of treatment with canagliflozin 100 mg and 300 mg once daily significantly reduced HbA1c (-0.77% and -1.03% respectively) in patients with T2DM not controlled with diet and exercise compared to placebo (0.14%, $P < 0.001$)[147]. Also, significantly reduced fasting blood glucose, -27 mg/dL to -34 mg/dL with both doses of canagliflozin (placebo = 9 mg/dL, $P < 0.001$). Get for this reason a larger number of patients in target HbA1c < 7.0% compared to placebo (44.5% to 62.4% *vs* 20.6%; $P < 0.001$). At week 52 in the double therapy, 300 mg canagliflozin under more HbA1c that sitagliptin (-0.73%, -0.88%, -0.73%, respectively)[148]. Data reduction in body weight with canagliflozin 100 and 300 mg *vs* placebo at week 26 were -3.7, -4.2, -1.2 kg, respectively ($P < 0.001$) and *vs* sitagliptin at week 52 were -3.8, - 4.2, -1.3 kg, respectively ($P < 0.001$). Also, in combination therapy, improved canagliflozin reducing body weight, HbA1c, and tolerance was better than in diabetics treated with metformin plus

sulfonylurea more than 52 wk[149]. At week 26, HbA1c decreased significantly with canagliflozin 100 and 300 mg *vs* placebo (-0.85%, -1.06%, -0.13%; $P < 0.001$); this improvement was maintained at week 52 (-0.74%, -0.96%, +0.01%). Both doses of canagliflozin (100 mg/d and 300 mg/d) showed non-inferiority in HbA1c reduction (-0.82% and -0.93%) compared to glimepiride for 52 wk of treatment in diabetic subjects treated with metformin. Canagliflozin 300 mg/d was more effective than glimepiride in decreasing HbA1c, and both doses of canagliflozin were higher than glimepiride in lowering body weight (-3.7 kg to 100 mg/d, -4.0 kg with 300 mg/d *vs* + 0.7 kg with glimepiride)[149]. Data from this study, objectified to 104 wk, showed that reductions in HbA1c remained with canagliflozin 100 and 300 mg and glimepiride *vs* placebo at week 104 (-0.65%, -0.55% and -0.76%), and both canagliflozin dose were better than glimepiride in weight reduction (-4.1 kg with 100 mg/d, -4.2 kg with 300 mg/d *vs* + 0.9 kg with glimepiride)[150].

Empagliflozin: Empagliflozin is a drug that has eight multinational clinical trials, including a very important safety trial of cardiovascular risk. Data empagliflozin 12 wk at doses 5-25 mg/d are increased excretion of glucose and a decrease of fasting blood glucose (-31.1 mg/dL. at 25 mg *vs* an increase +0.8 mg/dL. placebo), HbA1c (-0.63% *vs* 25 mg *vs* an increase of +0.09%) and body weight (-2.0 kg to 25 mg *vs* -0.8 kg) in T2DM[151]. Both doses of empagliflozin (10 mg or 25 mg daily) added to metformin received greater reductions in HbA1c *vs* sitagliptin (-0.34% to -0.63% *vs* -0.40%) and these were maintained for 90 wk. The fasting glucose reduction was also higher after 90 wk of treatment with two doses of empaglifozin against sitagliptin (-21 mg/dL and -32 mg/dL *vs* -16 mg/dL), and these effects were maintained over the treatment period[152]. The weight was reduced from the baseline of -2.2 to -4.0 kg with empaglifozin, -1.3 kg with metformin, and sitagliptin -0.4 kg after 90 wk[153]. In a randomized, double-blind empagliflozin (10, 25 mg) or placebo add-on to basal insulin for 78 wk; compared with placebo, 10 and 25 mg/d of empagliflozin significantly lower body weight (-2.2 kg, -2.0 kg, and +0.7 kg respectively), and decreased HbA1c (-0.48%, -0.64%, and -0.02%, respectively), and systolic blood pressure (-4.1 mmHg, -2.4 mmHg, and +0.1 mmHg, respectively)[154]. Therefore, a long-term empagliflozin is an effective treatment for patients with T2DM.

Pleiotropic effects: iSGLT2 achieve a decrease in body weight between 1-5 kg medium[155]. Weight loss is greater if, in addition, the use of these drugs able to decrease the dose of insulin. Patients fastest achieve greater weight reduction[156]. The results of studies over 4 years in T2DM patients treated with dapagliflozin *vs* glimepiride, both in combination with metformin, showed a reduction of 3.65 kg in the dapagliflozin group compared with the branch of glimepiride that gained an average of 0.73 kg[155]. There has been demonstrated in multiple studies that the loss of weight produced by these medicaments is principally secondary to a loss of fat mass (especially visceral abnormal fat) and not due to a volume depletion. Also, one has found a reduction of the abdominal perimeter[154]. In studies with canagliflozin it was observed that the 0.66% reduction in body weight was fat mass, and 0.33% was lean body mass. The association of iSGLT2 with anti-diabetic drugs that increase the weight (pioglitazone, insulin) can get minimize this gain[144]. iSGLT2 also reduce the systolic (-1.66 mmHg to -6.9 mmHg) and diastolic (-0.88 mmHg to -3.5 mmHg) blood pressure. This decrease occurs because the initial osmotic diuresis, and subsequent inhibition of the renin-angiotensin system[157], and the decrease is independent from the levels of glucose or from the weight of the patients. Also the effects on blood pressure were not dose-dependent and were not accompanied by any notable changes in heart rate or increases in hypotension and/or syncope[158,159]. Some analysis from phase IIb studies with empagliflozin revealed even greater decreases in systolic blood pressure of 13.4 mmHg to 17 mmHg amongst a subgroup of patients with a baseline systolic blood pressure > 140 mmHg compared to the overall population. In a study of dapagliflozin it was that the effects on blood pressure were more important in patients with a baseline systolic blood pressure > 140 mmHg.

It's not clear the effect of these medicaments on the lipid profile. The same results do not exist with all the iSGLT2. In some studies are lipid-friendly and in others are lipid-neutral drugs. Canagliflozin, for example, increases HDL cholesterol by 7.1%, LDL cholesterol by 7.1%, and reduces triglycerides by 2.3%, over 52 and 104 wk[160]. These modifications in lipid profiles were not observed with other iSGLT2 such dapagliflozin[161].

This new drugs also have a paper reducing the serum uric acid levels. They can decrease the levels in a range from -5.9% to -17.8% with the effect sustained for 2 years[162].

Finally, SGLT2 is associated with glomerular hyper-filtration; thus blockade of SGLT2 has potential nephr-oprotective action[163].

Side effects: The iSGLT2 has a similar incidence of adverse events in clinical trials which are given with other oral antidiabetic agents. The overall incidence of adverse events moves between 57.3% to 83.0%, and serious adverse events is between 1.0% and 12.6%[155].

Increased glucosuria produces the urogenital tract infections that are the most common side effects of these drugs[164], especially in women and uncircumcised men. Genital mycotic infections in women were vulvovaginal candidiasis, vulvitis, vulvovaginitis, and vulvovaginal mycotic infection. In male patients balanitis and balanoposthitis occur. In trials with dapagliflozin 2.5, 5 and 10 mg doses, the incidence of urogenital tract infections was 4.1%; 5.7% and 4.8% depending on the

dose of the drug *vs* 0.9% in placebo patients[165].

Another adverse effects of these agents also derived from his mechanism of action is the orthostatic hypotension and the volume depletion. These drugs are associated with an osmotic diuresis that can produce it. In randomized controlled trials the occurrence of these side effects was very low (< 3%)[166]. The extra diuresis experienced per day does not cause nicturia[167].

iSGLT2 have a non-insulin based mechanism and because of that the risk of hypoglycaemia is minimal with them. This risk can increase in therapy combined with sulfonylureas or insulin.

The use of iSGLT2 is associated with changes in bone turnover markers, with reduction in bone formation without changes in bone mineral density. There are long-term studies do not confirm these changes related to skeletal system[150,154]. A 2-year study with dapagliflozin, no objective changes in bone turnover markers compared with placebo when combined with metformin[162].

There have been reports of euglycaemic ketoacidosis in some patients treated with iSGLT2[168]. They are studying the mechanisms by which this complication may occur. This is frames ketoacidosis with blood glucose levels < 200 mg/dL. The possible cause of the euglycaemic ketoacidosis can be attributed to the recent use of insulin, reducing calorie intake, alcohol abuse, chronic liver disease and glycogen storage disorders[169].

Cardiovascular effects: All iSGLT2 have launched important studies of cardiovascular safety. It has now ended with empagliflozin conducted with promising results for this therapeutic group.

EMPA-REG is an international prospective, placebo-controlled trial of empagliflozin cardiovascular outcomes in patients with T2DM and know cardiovascular disease. In the trial he managed to reach the main objective of non-inferiority and also showed, after 3.1 years of median follow-up, the superiority of empagliflozin group (10 or 25 mg/d) *vs* placebo in what with respect to the primary composite cardiovascular endpoint (-14%), hospitalizations for heart failure (-35%), cardiovascular mortality (-38%) and mortality from all causes (-32%, each $P < 0.001$). The decrease in mortality appeared from early stages (< 6 mo) and referred to all subgroups, without any apparent heterogeneity. These reductions in mortality appear to be related to the diuretic and natriuretic effect of empagliflozin, and not with concomitant reductions in HbA1c, body weight, blood pressure, waist circumference and serum uric acid levels in the field of empagliflozin respect to placebo. Tolerance and safety of empagliflozin was good, objectifying only a moderate increase in benign genital fungal infections, adverse event known iSGLT2[170].

INJECTABLE AGENTS

RA-GLP1

Human GLP1 is secreted in response to food intake and stimulates insulin release[171]. Two incretins have been identified: GLP1, which is produced and released mainly by L-cells located in the distal ileum and GIP, which is secreted by enteroendocrine K-cells in the proximal gut.

GLP1 treatment in T2DM patients increased insulin secretion glucose dependent and decrease secretion of glucagon, slowed gastric emptying, raised satiety, and reduce food intake[172]. GLP1 also protect against myocardial ischemia[173,174]. In blood vessels promotes endothelium-independent artery relaxation protecting against endothelial dysfunction. Also have effect in protecting renal function by increasing diuresis and natriuresis[175,176]. All of these actions allow lower blood pressure and have positive effects on cardiovascular risk markers such as plasminogen activator inhibitor and brain natriuretic peptide.

The use of GLP1 therapy is limited by its rapid breakdown by DPP4; it has a short half-life: 1-2 min. Multiple RA-GLP1 have been developed with the physiological effects of GLP1 and an extended duration of action. RA-GLP1 agonists have proven efficacy for lowering HbA1c, fasting plasma glucose, body weight and systolic blood pressure, with a reduced risk of hypoglycaemia[6]. EASD/ADA and AACE guidelines recommended their use in combination with metformin, or as triple therapy in combination with metformin, sulfonylureas, TZD or insulin[9,42].

RA-GLP1 are classified by their duration in short-acting or long-acting. Short acting RA-GLP1 are exenatide twice daily and lixisenatide; their provide short-lived GLP1 receptor activation; tend to have a more accentuated effect on postprandial hyperglycaemia and gastric emptying and less effect on fasting glucose. Long acting RA-GLP1 are liraglutide, once-weekly formulation of exenatide Exenatide LAR), albiglutide and dulaglutide; they activate the GLP1 receptor continuously, compared with short-acting effect on gastric emptying and post-prandial glucose. Exenatide, exenatide LAR and lixisenatide derived from the exendin-4 molecule, a peptide with a 53% homology with human GLP1[177-179]. Liraglutide, albiglutide and dulaglutide are 97%, 95% and 90% identity.

Exenatide: Exenatide was the first RA-GLP1 to be approved for glycaemic control. Is a synthetic 39-amino acid peptide identical to the exendine-4 molecule isolated from salivary glands of the Gila monster; shares approximately 53% homology with native GLP1. The usual dose is 5-10 μg twice-daily subcutaneous injection.

Exenatide in monotherapy lowered HbA1c by 0.7%-0.9% and fasting plasma glucose by 17.5-18.7 mg/dL. The efficacy and safety of exenatide has been proved in several clinical studies[180-183]. Up to 46% of patients treated with exenatide achieved HbA1c ⩽ 7% objective compared with up to 13% of placebo group. Moreover, mean change in body weight from baseline was greater in the exenatide group (-1.6 to -2.8 kg) than in the placebo group (-0.3 to -0.9 kg)[180-182]. When

compared exenatide with insulin glargine or biphasic insulin aspart in patients with T2DM not controlled with oral agents, there were similar reductions in HbA1c in the exenatide and insulin groups (approximately -1.0%) suggesting non-inferiority of exenatide compared to insulin in relation to HbA1c reduction[184,185]. Exenatide showed weight loss and reduction in postprandial glycaemia compared with any insulin therapy, and lower rate of nocturnal hypoglycaemia compared with insulin glargine. In the glargine comparison study, insulin was titrated based upon achieving a target fasting glucose level < 100 mg/dL (5.6 mmol/L).

Lixisenatide: Lixisenatide is a RA-GLP1 that shares some structural elements with exendin-4. Compared with native GLP1, it has a prolonged half-life (2.7 to 4.3 h). Is available in Europe, not in United States, for use in combination with oral agents or insulin; is not considered a first-line therapy. Is available in a prefilled pen containing 14 doses of 10 or 20 mcg of lixisenatide. The initial dose is 10 mcg subcutaneously once daily within one hour prior to any meal of the day; after 2 wk the dose can be increased to 20 mcg.

Lixisenatide has been studied as monotherapy and in combination with one or two oral agents (metformin, pioglitazone, sulfonylureas). In a 24-wk double-blind trial of lixisenatide 20 mcg once daily *vs* placebo in 680 T2DM patients inadequately controlled with metformin (mean HbA1c 8.1%), the mean reduction in HbA1c was significantly greater with lixisenatide (-0.9% *vs* -0.4%)[186], and in another 24-wk no inferiority trial of once-daily subcutaneous lixisenatide 20 mcg once daily *vs* exenatide 10 mcg twice daily in 634 T2DM patients inadequately controlled with metformin alone (mean baseline HbA1c 8%), lixisenatide was no inferior to exenatide (mean change HbA1c -0.79% *vs* -0.96% with exenatide)[187].

Lixisenatide has been also used in combination with basal insulin therapy[188-190]. In a 24-wk double-blind trial, in 495 patients with T2DM not controlled with insulin glargine and metformin (mean HbA1c 8.4%), HbA1c reduction was significantly greater in the lixisenatide group compared to placebo (-0.6% *vs* -0.3%).

Liraglutide: Liraglutide is a human RA-GLP1, obtained through modifications of the human GLP1, with a large half life, which is administered once a day. Is available for use as monotherapy (adjunct to life style changes) or in combination with oral agents and basal insulin in adults with T2DM. The initial dose is 0.6 mg once daily subcutaneously the first week; and after the dose should be increased to 1.2 mg; and if HbA1c remain above the goal range the dose can be increased to 1.8 mg. It can be administered at any time of the day, with or without meals.

In clinical studies, administration of liraglutide (0.6-1.8 mg/d), alone or added to other antidiabetics agents, resulted in a reduction in HbA1c between 0.6%-1.6%. In a 52-wk trial of monotherapy with liraglutide (1.2 or 1.8 mg) *vs* glimepiride (8 mg) in 746 patients with recently diagnosed T2DM, the proportions of patients achieving an HbA1c $\leqslant$ 7% were 43%, 51% and 28%, respectively. Reductions in HbA1c were significantly greater with liraglutide 1.2 and 1.8 mg (-0.84% and -1.14% *vs* -0.51% with glimepiride). In addition, the HbA1c reduction with liraglutide (1.8 mg) was higher than that with other doses[191]. In another 26-wk double-blind trial, 413 T2DM patients not controlled with basal insulin and metformin were randomly assigned to exchange basal insulin with insulin degludec or insulin degludec plus liraglutide; all patients continued metformin[192]. The reduction in HbA1c was significantly greater in the degludec-liraglutide group (treatment difference -1.1%). The mean reduction in weight with degludec-liraglutide was 2.7 kg *vs* no change with degludec alone.

Exenatide LAR: Administration of exenatide LAR was proved more effective than highest dose of exenatide twice-daily[193,194], sitagliptin and pioglitazone[195], and insulin glargine[196] in T2DM patients treated with oral hypoglycaemic agents. Is available for use as adjunct to lifestyle changes to improve glycaemic control in T2DM. The usual dose is 2 mg subcutaneously once weekly at any time of the day with or without meals.

Albiglutide: It is a RA-GLP1 with a half-life of five to seven days, which allows once-weekly administration. It is available for use as monotherapy or in combination with oral agents or basal insulin. Is available in prefilled pen that contain a powder (30 or 50 mg), and a diluent to make a solution that is injected subcutaneously once weekly. The initial dose is 30 mg, and if after 6-8 wk blood glucose remain above the goal, the dose can be increased to 50 mg.

Albiglutide has been studied as monotherapy and in combination with one or two oral agents (metformin, pioglitazone, sulfonylureas and insulin). As examples: In a one-year trial of albiglutide *vs* insulin glargine in 779 T2DM patients inadequately controlled with metformin (with or without a sulfonylurea), the mean HbA1c reduced from 8.28% to 7.62% in the albiglutide group and from 8.36% to 7.55% in the glargine group[197]. Albiglutide met its pre-specified non-inferiority margin; however the comparison should be interpreted with caution because the dose of glargine was not systematically up titrated. Glargine was significantly more effective than albiglutide in reducing fasting blood sugar. In another two-year trial of weekly albiglutide *vs* daily sitagliptin, daily glimepiride, and weekly placebo in patients with T2DM inadequately controlled with metformin (mean HbA1c 9.1% to 8.2%), the reduction in HbA1c from baseline among the four groups was -0.6%, -0.3%, -0.4%, and +0.3%, respectively[198]. Although statistically significant, the mean reduction in HbA1c from baseline in the albiglutide group compared with the sitagliptin and glimepiride groups was small and of uncertain clinical relevance.

Dulaglutide: It is the last RA-GLP1 in appear. It has a structure that gives it the properties of slow absorption and reduced renal clearance rate. It is available for use as monotherapy or in combination with oral agents or insulin, in a ready-mixed pen at dose of 0.75 mg in monotherapy once weekly or 1.5 mg in combination, once weekly.

It has been compared with other antiabetic agents such metformin, iDPP4, insulin and other RA-GLP1, with a reduction in HbA1c ranging from -0.78% to -1.51%. In a 52-wk trial of weekly dulaglutide (0.75 or 1.5 mg weekly) *vs* sitagliptin in 1098 T2DM patients not controlled with metformin, the reduction in mean HbA1c was significantly greater with either dose of dulaglutide (mean HbA1c reduced from 8.2% to 7.3% with dulaglutide 0.75 mg weekly, from 8.1% to 7.0% with dulaglutide 1.5 mg weekly, and from 8% to 7.6% with sitagliptin)[199]. The mean change in body weight was significantly better with dulaglutide (-2.6 kg and -3 kg *vs* -1.53 kg with sitagliptin).

Precautions and side effects: All RA-GLP-1 should not be used in patients with history of pancreatitis and are not approved for use in T1DM. Exenatide and lixisenatide should not be utilized in patients with an eGFR < 30 mL/min and with severe gastrointestinal disease. Liraglutide, albiglutide and dulaglutide should not be used in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B.

The mayor side effect are gastrointestinal, particularly nausea, vomiting and diarrhoea. It appears with lower frequency with exenatide LAR or lixisenatide than exenatide twice daily; albiglutide had lower rates than liraglutide and liraglutide and dulaglutide are similar. The risk of hypoglycaemic events is small, and may occur when RA-GLP-1 is given in conjunction with other treatments that cause hypoglycaemia, *e.g.*, basal insulin, sulfonylureas.

Injection site reactions are more common with RA-GLP-1 than with insulin. Between RA-GLP1 are more common with exenatide LAR and with albiglutide. These reactions can be abscess, cellulitis and necrosis with or without subcutaneous nodules. Antibodies to RA-GLP1 may occur. In the majority of patients, the titre of antibodies decreases over time and does not affect glycaemic control. In a meta-analysis of 17 trials, the proportion of patients with antibodies against RA-GLP1 was higher in the albiglutide group compared with placebo (6.4% albiglutide 30 mg weekly *vs* 2% with placebo)[200].

Head-to-head comparisons of RA-GLP1: They have been published 9 phase III clinical trials, comparing different pairs of RA-GLP1[201]. One of them is with taspoglutide: T-emerge 2; we are not going to include it in the present review because it development was halted because of serious hypersensitivity reactions and gastrointestinal adverse events.

DURATION-1[193]: Exenatide twice daily *vs* exenatide LAR. Duration: 30 wk. Inclusion criteria: ⩾ 16 years, therapy with lifestyle changes, or with 1-2 oral agents (metformin, sulfonylureas and/or TZD), HbA1c 7.1%-11.0%, fasting plasma glucose < 16 mmol/L, and body mass index (BMI) 25-45 kg/m^2.

DURATION-5[194]: Exenatide twice daily *vs* exenatide LAR. Duration 24 wk. Inclusion criteria: ⩾ 18 years, therapy with lifestyle changes, or with metformin, sulfonylureas, TZD or a combination, HbA1c 7.1%-11.0%, fasting plasma glucose < 15.5 mmol/L, and BMI 25-45 kg/m^2.

DURATION-6[202]: Exenatide LAR *vs* liraglutide once daily. Duration 26 wk. Inclusion criteria: ⩾ 18 years, therapy with lifestyle changes and oral agents (metformin, sulfonylureas, metformin + sulfonylureas or metformin + pioglitazone), HbA1c 7.1%-11.0%, and BMI ⩽ 45 kg/m^2 and stable body weight.

LEAD-6[203]: Exenatide twice daily *vs* liraglutide once daily. Duration 26 wk. Inclusion criteria: 18-80 years, treated with metformin, sulfonylureas or both, HbA1c 7.0%-11.0%, and BMI ⩽ 45 kg/m^2.

GetGoal-X[188]: Exenatide twice daily *vs* lixisenatide once daily. Duration 24 wk. Inclusion criteria: 21-84 year, therapy with metformin, and HbA1c 7.0%-11.0%.

HARMONY 7[204]: Albiglutide once weekly *vs* liraglutide once daily. Duration 32 wk. Inclusion criteria: ⩾ 18 years, therapy with metformin, sulfonylureas, TZD or a combination, HbA1c 7.0%-10.0%, and BMI 20-45 kg/m^2.

AWARD-6[205]: Dulaglutide once weekly *vs* liraglutide once daily. Duration 26 wk. Inclusion criteria: ⩾ 18 years, therapy with metformin, and HbA1c 7.0%-10.0%.

Kapitza *et al*[206]: Lixisenatide once daily *vs* liraglutide once daily. Duration 28 wk. Inclusion criteria: 37-74 years, therapy with metformin, and HbA1c 6.5%-9.0%.

Effects on HbA1c: In the DURATION-1 and DURATION-5 exenatide LAR produced more consistent and greater reductions in HbA1c than exenatide twice daily. In the GetGoal-X exenatide twice daily showed greater HbA1c reduction than lixisenatide. Liraglutide in LEAD-6 and DURATION-6 reach greater HbA1c reductions tan exenatide twice daily or exenatide LAR, and in HARMONY 7 shows also greater reductions tan albiglutide. Liraglutide and dulaglutide did not differ in AWARD-6 study.

Effects on weight: It varies among RA-GLP1 and studies. In DURATION-1 and DURATION-5, there were no significant differences in weight loss between the two exenatide preparations. In LEAD-6, liraglutide and exenatide twice daily loss similar weight as in GetGoal-X study, between exenatide twice daily and lixisenatide, the difference was non-significant. Only in AWARD-6 and in the study by Kapitza *et al*[206], liraglutide revealed significantly greater reductions than dulaglutide and lixisenatide.

Cardiovascular effects: Improvements in both systolic and diastolic blood pressure have been reported in clinical trials; however in these head-to-head trials there were no statistically significant differences between treatments. Increases in resting heart rate have been reported. With exenatide twice-daily the

Table 5 Type of insulin by onset of action, peak effect and duration of action

Insulin type	Onset of action	Peak effect	Duration of action
Lispro, aspart, glulisine	5 to 15 min	45 to 75 min	2 to 4 h
Regular	About 30 min	2 to 4 h	5 to 8 h
NPH	About 2 h	4 to 12 h	18 to 28 h
Insulin glargine	About 2 h	No peak	20 to 24 h
Insulin detemir	About 2 h	No peak	6 to 24 h[1]
NPL	About 2 h	Six hours	15 h
Insulin degludec	About 2 h	No peak	> 40 h
Insulin U-300	About 2 h	No peak	> 36 h

[1]Duration of action is dose-dependent. At higher doses (≥ 0.8 units/kg), mean duration of action is longer and less variable. Modified from: McCulloch DK. General principles of insulin therapy in diabetes mellitus. Uptodate, March 24, 2016. Available from: URL: http://www.uptodate.com/contents/general-principles-of-insulin-therapy-in-diabetes-mellitus.

heart rate increases, but it is lower than with exenatide LAR or liraglutide; dulaglutide is similar to liraglutide. With lixisenatide and albiglutide has not shown an increase in heart rate.

Insulin

Insulin is utilized in the treatment of patients with all types of diabetes[207]. Human insulin preparations (NPH and regular insulin) do not imitate endogenous insulin secretion (basal and postprandial). Then, insulin analogues (aspart, lispro, glulisine, detemir, glargine, degludec and U-300) were developed. They have increased the flexibility and efficacy of diabetes management. The very rapid-acting insulin analogs have both: Faster and shorter duration of action than regular insulin for pre-meal coverage, while the long-acting analogs have a longer duration of action allowing once-daily dosing; also shows less day-to-day variability[208] (Table 5).

Insulin preparations: Long-acting insulins (glargine and detemir), and ultra-long-acting insulins (degludec and Glargine U-300) can be combined with rapid-acting insulins (aspart, lispro or glulisine) in basal bolus therapy.

Insulin glargine and human insulin are the same except for a substitution of glycine for asparagine in position A21 and by the addition of two arginine molecules in the B-chain of the insulin molecule[209]. These modifications originate a change in the pH such that, after administration, glargine precipitates in the subcutaneous tissue making hexamers, which delays absorption and extends duration of action. Glargine has a duration of action that usually lasts 24 h. Glargine cannot be mixed with rapid-acting insulins as the kinetics of both the rapid acting insulin and glargine and will be modified.

Insulin detemir is another insulin analog developed by removing a threonine an acylating a lysine with 14-carbon fatty acid; the fatty acid side chain allows albumin binding and results in prolongation of action. Clinical trials in patients with type 1 diabetes have suggested that twice-per-day injections may be necessary to achieve acceptable basal rate coverage and optimal glycaemic control[210]. In T2DM, where endogenous insulin secretion may mask any deficiencies in basal insulin, the data are less clear. Nevertheless the duration of action is dose-dependent; at higher doses mean duration of action is longer. Detemir cannot be mixed with rapid-acting insulins.

When glargine and detemir are administered in high doses, both show a peak on pharmacokinetic and pharmacodynamics profile[211]; also there is still interindividual variability and low doses are insufficient to cover a 24-h period[212]. Therefore, new ultra-long insulins were developed: Degludec, glargine U300 and LY2605541 (PEGylated Lispro). Lilly had discontinued the development of the last one because of hepatic lipid accumulation.

Insulin degludec is a modified B chain analogue that forms hexamers and di-hexamers when is administrated. Compared with other long-acting insulins (glargine and detemir), the insulin degludec profile is flatter with a half life greater than 25 h, and action that exceeds 42 h, which results in a reduction of confirmed and nocturnal hypoglycaemias[213]. Glargine U300 is the same glargine molecule concentrated three times; so it has the same mechanism to slow its absorption as insulin glargine.

At present there are no head-to-head comparisons of insulin degludec and Glargine U-300. We are going to analyse clinical trials of both of them but comparisons between them should not be make because the studies are different: for example hypoglycaemia definition use in degludec is plasma glucose threshold of 3.1 mmol/L (55.85 mg/dL) and in Glargine U-300 is 3.9 mmol/L (70.26 mg/dL).

Clinical trials in T2DM: BEGIN basal-bolus type 2 study is a 52-wk, randomised, treat-to-target, parallel-group, open-label, non-inferiority trial. Compared the efficacy and safety of once-daily insulin degludec with once-daily insulin glargine in a basal-bolus regimen with mealtime insulin aspart, with or without metformin, pioglitazone, or both in participants with T2DM[214]. After 1 year, HbA1c decreased by 1.1% in the degludec group and 1.2% in the glargine group. Rates of overall confirmed hypoglycaemia (plasma glucose < 55 mg/dL) were lower with degludec, as well as rates of confirmed nocturnal hypoglycaemia. These results were maintained in a 26-wk extension of this study with fewer hypoglycaemic episodes (24% overall reduction and 31% confirmed nocturnal episodes reduction)[215].

BEGIN Once Long was a 1 year phase 3 trial with type 2 insulin naive patients not controlled with oral hypoglycaemic agents. Again insulin degludec shows non inferiority in reducing HbA1c, and demonstrate a lower rate of nocturnal hypoglycaemia compared with

glargine[216].

EDITION 1, 2 and 3[217-219] evaluated Gla-U300 in T2DM patients through 6 mo. The primary endpoint in the three studies was meeting the non-inferiority criterion in reduction HbA1c levels; which is confirmed in all studies; and the secondary endpoint was the percentage of patients with one or more confirmed or several nocturnal hypoglycaemias between week 9 and month 6. In EDITION 1 fewer patients reported one or more confirmed (< 3.9 mmol/L or < 70 mg/dL) or severe nocturnal hypoglycaemic events between week 9 and month 6 with Gla-U300 [36% *vs* 46% with Gla-U100; relative risk 0.79 (95%CI: 0.67-0.93); P < 0.005]. In EDITION 2, again the percentage of patients with nocturnal hypoglycaemia was lower in those with Gla-U300 than with Gla-U100 with a risk reduction of 23%. In EDITION 3, the percentage of patients with nocturnal hypoglycaemia was statistically similar in patients with Gla-U300 and Gla-U100.

In conclusion, insulin degludec showed similar efficacy in reducing HbA1c to insulin glargine, with a decreased risk of confirmed and nocturnal hypoglycaemia.

OTHER TREATMENTS

Colesevelam

Colesevelam is a bile acid sequestrant that reduces LDL cholesterol in patients with hypercholesterolemia.

Mechanism of action: Possibly colesevelam interferes glucose absorption at gastrointestinal level.

Efficacy: In T2DM patients not controlled, colesevelam added to treatment of oral hypoglycaemic agents or insulin resulted in a reduction of HbA1c levels of 0.5%[220-222].

Side effects: nausea, constipation and dyspepsia are frequent side effects. Also increases triglyceride concentrations by approximately 20%. We do not recommend colesevelam to treat T2DM patients due the modest glucose-lowering effectiveness, expense, and limited clinical experience.

Bromocriptine

Bromocriptine is a dopamine agonist that has been used for the treatment of hyperprolactinemia and Parkinson disease.

Mechanism of action: The mechanism of action in reducing blood glucose is unknown. A quick release formulation of bromocriptine (Cycloset) was approved by the FDA for the treatment of T2DM[223].

Efficacy: In short-term clinical trials in T2DM patients, bromocriptine (up to 4.8 mg daily) as monotherapy or added to sulfonylureas reduce HbA1c compared with placebo in 0.4%-0.5%[223,224].

Side effects: Nausea, vomiting and headache[225] are frequent side effects. We do not recommend bromocriptine to treat T2DM patients due its glucose lowering effect and very frequent side effects.

Pramlintide

Pramlintide is an amylin analog that is administered by mealtime subcutaneous injection. It is available for use for both T1 and insulin-treated T2DM; is only be used in patients also taking prandial insulin. Pramlintide replicates amylin actions and controls glucose without causing weight gain.

Mechanism of action: Pramlintide control postprandial blood glucose levels by slowing gastric emptying, promoting satiety, and reducing the postprandial glucagon increase in patients with diabetes[226]. The effects are glucose-dependent. Pramlintide does not cause hypoglycaemia in the absence of therapies that may cause hypoglycaemia. Supraphysiologic doses of pramlintide do not provoke hypoglycaemia in normal subjects, and pramlintide does not interfere with recovery from insulin-induced hypoglycaemia[227].

Efficacy: There are several randomized controlled trials in T2DM that shows its efficacy; for example when added pramlintide to existing insulin therapy with or without a sulfonylurea or metformin, reductions in HbA1c (mean 0.62%) and weight (1.4 kg) were seen with 120 mcg but not 90 mcg of pramlintide given twice daily[228]. In a 24-wk trial or without oral agents had similar glycaemic efficacy as the addition of premeal rapid acting insulin analogs (HbA1c reduction of approximately 1%)[229]. Patients randomly assigned to pramlintide maintained their weight, whereas those assigned to rapid acting insulin gained weight (mean 4.7 kg). Pramlintide was associated with fewer hypoglycaemic events compared with prandial insulin. In addition to modest reductions in HbA1c and body weight, pramlintide has been associated with reductions in postprandial glucose excursions and in surrogate markers of cardiovascular risk and oxidative stress[230,231].

Side effects: The most frequent side effect is nausea and generally dissipates by four weeks. Pramlintide should not be administered to patients with severe hypoglycaemia unawareness. Pramlintide should only be administered before meals that contain at least 250 calories or 30 g of carbohydrates. The recommended initial dose for T2DM is 60 mcg, titrated upward as tolerated to 120 mcg with each meal.

TREATMENT OF T2DM IN OLDER PATIENTS

Elderly people with diabetes have a risk of developing macrovascular and microvascular complications, similar

to that of younger patients with diabetes. In addition, they have a higher rate of lower limb amputations, and other complications than any other age group[232,233]; and those ⩾ 75 years have a higher rate of most complications than those between 65 and 74 years. Older people > 75 years have a significant increase in death by hypoglycaemia, and visits to the emergency room for hypoglycaemia, compared to the general population with diabetes[234].

Therefore, older people with diabetes have a number of characteristics that will influence their treatment, such as[235]: (1) presence of high co-morbidities; (2) presence of cognitive and functional impairment (falls); (3) polypharmacy; (4) visual and hearing impairment; (5) decreased physical activity; (6) high risk of hypoglycaemia; (7) common situations of social isolation and dependence. Depression; (8) nutrition-related problems; and (9) heterogeneity in terms of clinical presentation of the diabetes (diabetes duration, co-morbidities, functional status, life expectancy).

Based on all the above, the treatment of diabetes in the elderly people should achieve the following objectives: (1) to avoid disability, ensuring the best quality of life; (2) to avoid side effects of treatment, especially the most associated with impaired quality of life such as hypoglycaemia and falls; and (3) to have a global vision of the patient, introducing competitive risks in the decision-making process.

The initial treatment of T2DM in elderly patients is similar to that of younger patients, and includes changes in the lifestyle, with weight reduction, although most of elderly patients with T2DM will need drug treatment throughout his life.

Lifestyle modification

Changes in lifestyle are very important in the treatment of diabetes at any age, but they deserve special considerations for the elderly. In the Diabetes Prevention Program, people < 60 years of age improved their glycaemic control over time, due in part to better adapt to changes in lifestyle, compared with other younger age groups[236,237].

Nutritional needs: Although calorie needs decrease with age, macronutrient needs will be similar throughout adulthood. Older people with diabetes are at risk of malnutrition from anorexia, altered taste and smell, difficulty swallowing, oral and dental problems, and functional alterations; major difficulties in the preparation and consumption of food. The Mini Nutritional Assessment, a questionnaire designed to detect malnutrition, is very easy to use and has proved useful in diabetics elderly patients[238].

Nutritional recommendations should take into account the customs of the patients, their preferences and their personal goals and skills. When the regular intake does not meet the nutritional needs, a number of modifications, such as recommending fewer meals but more frequent, change the texture of foods, fortifying common foods, or add nutritional supplements between meals will be necessary. Overweight and obesity are common among the elderly. BMI is not useful in some older people due to changes in body composition with age[239]. Sarcopenia can occur in either overweight or underweight elderly. Moreover, obesity is often accompanied by decreased physical activity and increased frailty[240]. The unintentional weight loss in overweight or obese older people could worsen sarcopenia, bone mineral density and nutritional deficits[241,242]. Strategies that combine physical activity with nutritional therapy in older patients with diabetes, will lead to improved physical performance and a reduction of cardiometabolic risk[240,241].

The caloric intake in the elderly should be between 25 and 35 kcal/kg per day[243]. Protein should provide 15%-20% of total calories, fat 30% maximum, avoiding saturated fats and trans fats, and promoting the consumption of monounsaturated fats and omega 3 fatty acids, and carbohydrates 50%-55% based on complex carbohydrates. A dietary fiber intake of about 14 g/1000 kcal is recommended, and they may also require calcium and vitamin D and vitamin B12 supplements. Fluid intake should be 30 mL/kg per day, with a minimum intake of 1500 mL/d, which may be increased in situations such as fever, infections, high temperatures, or excessive losses in urine and feces; or decreased in case of advanced renal insufficiency, or in states of fluid retention such as heart failure and liver cirrhosis[243].

Physical activity: In older people with diabetes, muscle mass and strength decrease with age, worsening by complications of diabetes, co-morbidities and hospitalizations. People with diabetes of long duration and high levels of HbA1c, have less muscle strength per unit of muscle mass, that people without diabetes of similar age and BMI, and that people with diabetes of short duration and better glycaemic control[244]. Increased physical activity will improve the functional status of the elderly with or without diabetes[245]. In the elderly, mild physical activity is related with increased physical health and psychosocial well-being[246], so that in these people with diabetes, healthy, it is recommended to perform the same exercise as other adults with diabetes[42]. Older patients with poorer health, will benefit even a modest increase in physical activity. Finally, patients at risk of falls should be referred to a physiotherapist for muscle and exercise balance.

Pharmacologic treatment

Older patients have an increased risk of adverse events related to drugs due to pharmacokinetic changes as decreased renal elimination, and pharmacodynamics changes, age related, such as increased sensitivity to certain medications, which can affect at their disposal. These changes may result in an increased risk of hypoglycaemia, the need to reduce the dose of certain medicines and monitor renal function to minimize

adverse effects[247,248]. It is important to select drugs with a strong benefit/risk ratio, to provide efficacy, persistence and safety of treatment. Usually, in older people with diabetes is recommended to start treatment with antidiabetic at low doses, and titrate the dose progressively according to response, without reaching the maximum dose, due to the risk of increased side effects without increasing efficiency[249].

Knowledge of the advantages and disadvantages of each family of antidiabetic drugs will help clinicians individualize treatment of elderly patients with T2DM[6].

Metformin: Metformin remains the drug of choice for first-line treatment of T2DM in any age group, including the elderly. Its low risk of hypoglycaemia, its potential benefits in patients with stable cardiovascular disease[250] or heart failure, and its low cost, makes it a beneficial drug for older people. However its side effects such as gastrointestinal intolerance, vitamin B12 deficiency and weight loss, do not recommend its use in frailty patients. Although the risk of lactic acidosis is minimal, it is recommended to monitor renal function frequently, reduce the dose if the eGFR is between 30-60 mL/min[242], and do not use it with eGFR < 30 mL/min[249-251]. Moreover, metformin should not be used in situations of tissue hypoxia, acute intercurrent disease, respiratory failure, acute heart failure, hepatic failure, administration of iodinated contrast, and risk of functional renal impairment (vomiting, diarrhoea). It is recommended to start with a low dose of 425 mg/d and titrate up to 1700 mg/d maximum, because with higher doses does not increase efficiency but increases side effects.

Sulfonylureas: They are also cheaper drugs, but due to its high risk of hypoglycaemia, should be utilized carefully in elderly. Hypoglycaemia appears more frequently with long-acting sulfonylureas such as chlorpropamide, glibenclamide and glimepiride, especially in older adults who develop severe and prolonged hypoglycaemia. We must stop using long-acting sulfonylureas in older adults[252], being preferable the use of shorter-acting sulfonylureas such as gliclazide and glipizide[253]. Circumstances that influence the occurrence of sulfonylureas-induced hypoglycaemia in the elderly are: (1) after exercise; (2) missed meals, eat poorly, without meal time, or abuse alcohol; (3) existence of impaired renal or cardiac function or intercurrent gastrointestinal disease; (4) after being in the hospital[254]; and (5) by associating salicylates, sulfonamides, fibric acid derivates such as gemfibrozil, and warfarin[255].

On the other hand, these drugs produce weight gain, and its use is limited in renal failure because of the high risk of hypoglycaemia. Furthermore, the large amount of drug interactions, interfere their use in the elderly.

Meglitinides: Repaglinide and nateglinide are designed to control postprandial glycaemia, so that its duration is short and they require more frequent administrations with meals than sulfonylureas. Moreover, are more expensive, which limits its use in older people, especially in patients with polypharmacy. They lead a lower risk of hypoglycaemia than sulfonylureas[256], especially in patients who do not a set meal schedule[72], but they have a similar risk for weight gain. In addition, repaglinide, for its mainly biliary elimination, can be utilized in patients with moderate or advanced renal impairment[257], and could be utilized as first-line in patients with impaired renal function when they are intolerant to metformin and sulfonylureas, or are contraindicated. It should not be associated with drugs that act by activating or inhibiting cytochrome P450, such as gemfibrozil, because of the high risk of hypoglycaemia.

Alpha-glycosidase inhibitors: Acarbose and miglitol are drugs that are intended to control postprandial blood glucose, with low risk of hypoglycemia, which are theoretically attractive to treat older people[258]. However gastrointestinal effects, low efficiency, more frequent daily doses, and cost limit their use. They can alter the levels of digoxin and acenocumarol.

Thiazolidinediones: Although TZD do not increase the risk of hypoglycaemia, and pioglitazone may be beneficial in patients in secondary prevention[259], the high cost and side effects that induce as weight gain, macular oedema, fluid retention, increased risk of heart failure and bone fractures, and possible risk of bladder cancer[260], limit their use in the elderly[261].

DPP-4 inhibitors: iDPP4 inhibitors are once-a-day oral agents which can be used safely in elderly patients**.** They are very beneficial agents for the treatment of T2DM in the elderly since they control both basal and postprandial hyperglycaemia, with good tolerability, low risk of hypoglycaemia, and without significant drug interactions, or weight gain. These agents do not require dose adjustment in patients with advanced age. Although vildagliptin has demonstrated efficacy and safety in patients $\geqslant$ 75 years[262], data safety in these patients is very limited. Linagliptin do not require dose adjustment in patients with renal impairment; vildagliptin at doses of 50 mg/d can be employed at any degree of renal failure; saxagliptin half-dose (2.5 mg/d) can be used in ESRD; and sitagliptin dose should be adjusted to the degree of renal insufficiency: 50 mg/d if the eGFR is between 30-50 mL/min, and 25 mg/d if < 30 mL/min. Finally, vildagliptin requires monitoring of liver function.

iSGLT2: The iSGLT2 dapagliflozin, canagliflozin and empagliflozin, represent a new class of oral hypoglycaemic agents that increase the urinary excretion of glucose. This effect results in lower blood glucose levels in an insulin-independent manner, with a lower risk of hypoglycaemia, as well as mild diuresis[263]. The

increase in glycosuria and diuresis produced, results in a reduction in weight and blood pressure. Because of these actions can be very attractive in the treatment of T2DM in the elderly[264,265]. However should not be utilized with an eGFR < 60 mL/min. Moreover, by inducing osmotic diuresis may increase the risk of dehydration, electrolyte abnormalities and weight loss that could limit its use in frail elderly patients. A common side effect of iSGLT2 is an increased incidence of genital and urinary infections, so they must be used with caution in elderly patients at increased risk of developing these infections or those with urinary incontinence[266].

RA-GLP1: The RA-GLP1 exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide, will control both basal and postprandial hyperglycaemia with a low risk of hypoglycaemia. The drug-related effects such as nausea, vomiting, decreased appetite and weight loss can be a problem for frail elderly patients; however may be an option in those not vulnerable, obese elderly patients with good performance status where weight loss is a priority[200], as in those with knee osteoarthritis, sleep apnoea syndrome, hypoventilation, etc. Its use is not recommended in patients with an eGFR < 50 mL/min. There is little experience in patients ⩾ 75 years, and its high cost and subcutaneous administration will limit its use in older patients.

Insulin: Insulin treatment can be utilized to achieve the goals of glycaemic control in selected older patients with T2DM, with similar efficacy and risk of hypoglycaemia than in younger patients. Before prescribing insulin in elderly subjects, we should think about the risk of hypoglycaemia related with this agent. The use of multiple daily injections of insulin, or by continuous subcutaneous insulin infusion in healthy elderly patients (mean age 66 years), has proven to be effective with a low rate of hypoglycaemia[267]. Also, the addition of long-acting insulin in elderly patients with T2DM (mean age 69 years) was as effective in achieving the HbA1c goals, without increased rate of hypoglycaemia, than in younger people (mean age 53 years)[268]. However there are few publications on the use of these insulin regimens in patients ⩾ 75 years or in elderly patients with several co-morbidities, and/or a functional limitation. Visual or manual dexterity problems can be difficult to insulin therapy in some older patients. The use of insulin delivery devices will facilitate this work, selecting the one that best suits the skills and abilities of the patient. The risk of hypoglycaemia and weight gain will be lower with the use of insulin analogues compared to human insulins, and are preferred in elderly, despite their higher cost[208,269], especially if there is a high risk of hypoglycaemia as in the frail or institutionalized elderly. Also, when necessary, the insulin analogs are preferable to short regular human insulin, due to its lower rate of hypoglycaemia[270]. Insulinization, especially in frail elderly, should start with a single daily dose of long-acting insulin (0.1-0.2 IU/kg), lower than in younger patients, to avoid hypoglycaemia. Figure 1 shows the International Diabetes Federation Global Guidelines for managing older people with T2DM[271].

TREATMENT OF T2DM IN PATIENTS WITH CKD

Before choosing a hypoglycaemic agent, we must consider the existence of an impairment renal function (Figure 2). Management of T2DM in patients with renal impairment is a complex process that requires a comprehensive approach. Clinicians must be aware that as renal function worsens, abnormalities in glucose homeostasis develop, affecting secretion, clearance, and peripheral tissue sensitivity to insulin[272]. CKD diagnosis adds risk factors for hypoglycaemia to those already present in patients with diabetes due to accumulation of uremic toxins, which lead to lower hepatic and renal insulin degradation, and also as a result of decreased renal gluconeogenesis, uremic malnutrition, and deficient catecholamine release[273]. Some of the additional factors are altered drug metabolism, drug-drug interactions, albuminuria, autonomic neuropathy, anorexia, malnutrition, infections, problems linked to dialysis, related cardiac and hepatic disease, and impaired renal glucose release[274,275]. On the other hand, both hypoglycaemia and CKD are related with increased morbidity and mortality from cardiovascular disease[276-278]. Many drugs are available for treatment of T2DM. Although all drugs can be utilized in patients with mild renal impairment[6,279], therapeutic choices for patients with moderate to severe CKD and ESRD are reduced, since drug or metabolite accumulation may occur due to a reduced GFR resulting in increasing side effects. In this case, some drugs are not recommended, while others can be used with dose adjustment.

Pharmacologic treatment

Metformin: The incidence of lactic acidosis in the setting of metformin therapy is low, and the drug is not necessarily responsible when lactic acidosis occurs in patients taking this medication[65]. Although drug levels are higher in those with kidney disease, levels are still maintained largely within the therapeutic range[280,281] and lactate levels are not substantially increased when metformin is utilized in those with reduced GFR[282-285]. The recommendations for use of metformin based on eGFR are shown in Figure 3[247]. However, the main problem for metformin treatment in CKD patients is the prevention of intoxication. Dosage guidelines for CKD patients have recently been published[286]. These recommend the following maximum daily doses related to creatinine clearance: 3 g (120 mL/min); 2 g (60 mL/min); 1 g (30 mL/min); 500 mg (15 mL/min). Moreover, Lipska *et al*[247] have proposed a possible approach to metformin prescribing in the setting of CKD. The physician contemplating metformin treatment

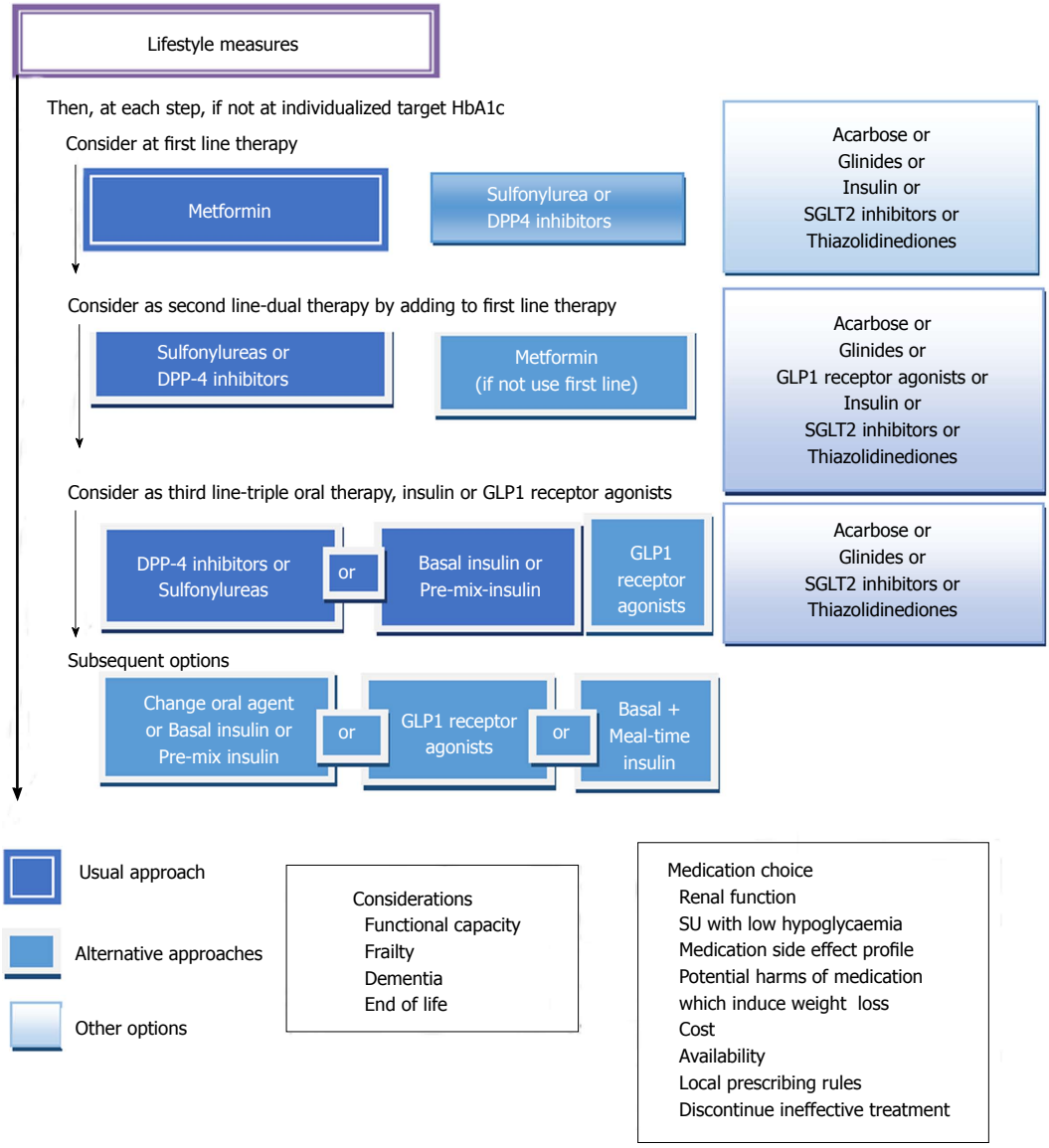

Figure 1 Global Guidelines for managing older people with type 2 diabetes. International Diabetes Federation[272]. SGLT2: Sodium glucose co-transporter-2; GLP-1: Glucagon-like peptide-1; DDP-4: Dipeptidyl peptidase-4.

in a CKD patient should also address other problems. He should be advised to temporarily cease therapy if he develops sudden weight loss or acute illness, particularly if accompanied by vomiting and diarrhoea. X-ray contrast can occasionally cause acute renal insufficiency. In accordance with recent guidelines[287], patients with an eGFR < 45 mL/min should stop metformin 48 h before contrast investigations, and restart 48 h after. Other contraindications, *e.g.*, liver disease and pregnancy, remain.

Sulfonylureas: Sulfonylureas can cause unregulated insulin release and lead to severe hypoglycaemia that can be particularly serious in the presence of CKD[288], due to the accumulation of active metabolites. Long-acting sulfonylureas like glyburide and chlorpropamide are more notorious for causing hypoglycaemia[289]. Shorter-acting sulfonylureas as glimepiride, glipizide and gliclazide agents are relatively safe and preferred in patients with CKD[290]. Major therapeutic considerations of sulfonylureas in patients with CKD and diabetes are[279,291-293]: (1) Glibenclamide should be prescribed with caution in patients with an eGFR 60-90 mL/min, and cannot be used in patients with an eGFR < 60 mL/min; (2) Glimepiride can be utilized in patients with an eGFR of < 60 mL/min, and dosage adjustment is required if the eGFR is < 30 mL/min. Begin at 1 mg daily or switch to another drug if the eGFR is < 15 mL/min; (3) Gliclazide is less than 1% excreted unchanged by the kidneys and does not have active metabolites[294]. It is recommended in subjects with an eGFR of 30-60 mL/min, need to reduce dose if the eGFR is < 30 mL/min, and it's not recommended if the eGFR is < 15 mL/min; and (4) Glipizide does not increase hypoglycaemia in patients with CKD. Can be utilized in all stages of CKD with caution and with dose reduction.

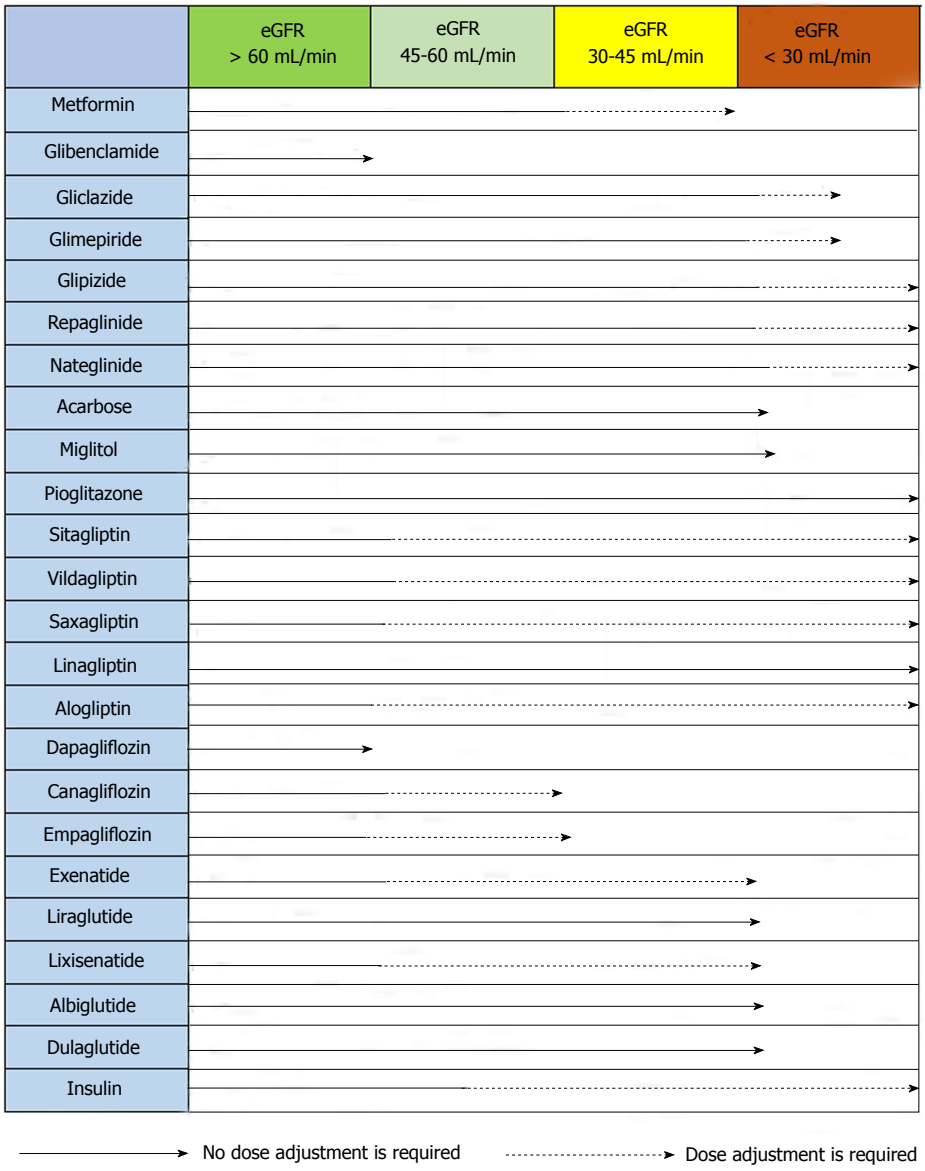

Figure 2 Recommendations for use of antidiabetic agents based on estimated glomerular filtration rate. Adapted from Zanchi *et al*[292]. eGFR: Estimated glomerular filtration rate.

Meglitinides: Both repaglinide and nateglinide are primarily metabolized in the liver, and generally, dose adjustment is not required for either of these agents. Therefore, their risk of hypoglycaemia is lower, and they are more effective for postprandial glycaemic control. Thus, at first, they may be employed in patients with CKD, without dose adjustment[295]. Repaglinide is mostly metabolised by the liver and could therefore be utilized in patients with low renal function, although some dose adjustment is required[296]. Nateglinide is rapidly degraded by the liver to mostly inactive or weakly active metabolites which are eliminated in the urine[297], also so can be considered patients with poor renal function, again with dose reduction. In conclusion, repaglinide and nateglinide can be prescribed in all stages of CKD with caution and dose reduction is necessary if the eGFR is < 30 mL/min[279,291,297,298].

Alpha-glucosidase inhibitors: As only less than 2% of an oral dose of acarbose was absorbed as active drug, patients with an eGFR < 25 mL/min attained increases about fivefold higher for peak plasma concentration of acarbose and six fold higher for AUC values than subjects with normal renal function[95]. Miglitol is systematically absorbed but is no metabolized, and is rapidly eliminated by renal excretion as unchanged drug[299]. Patients with an eGFR < 25 mL/min taking miglitol 25 mg three times daily showed a twofold increase in miglitol plasma levels when compared with patients with an eGFR > 60 mL/min[300]. Voglibose, an alpha-glucosidase inhibitor only commercialized in Japan, has no renal excretion, and two studies showed that it can be safely utilized in diabetic patients on haemodialysis, in combination with pioglitazone or mitiglinide[300,301]. In conclusion, alpha-glucosidase

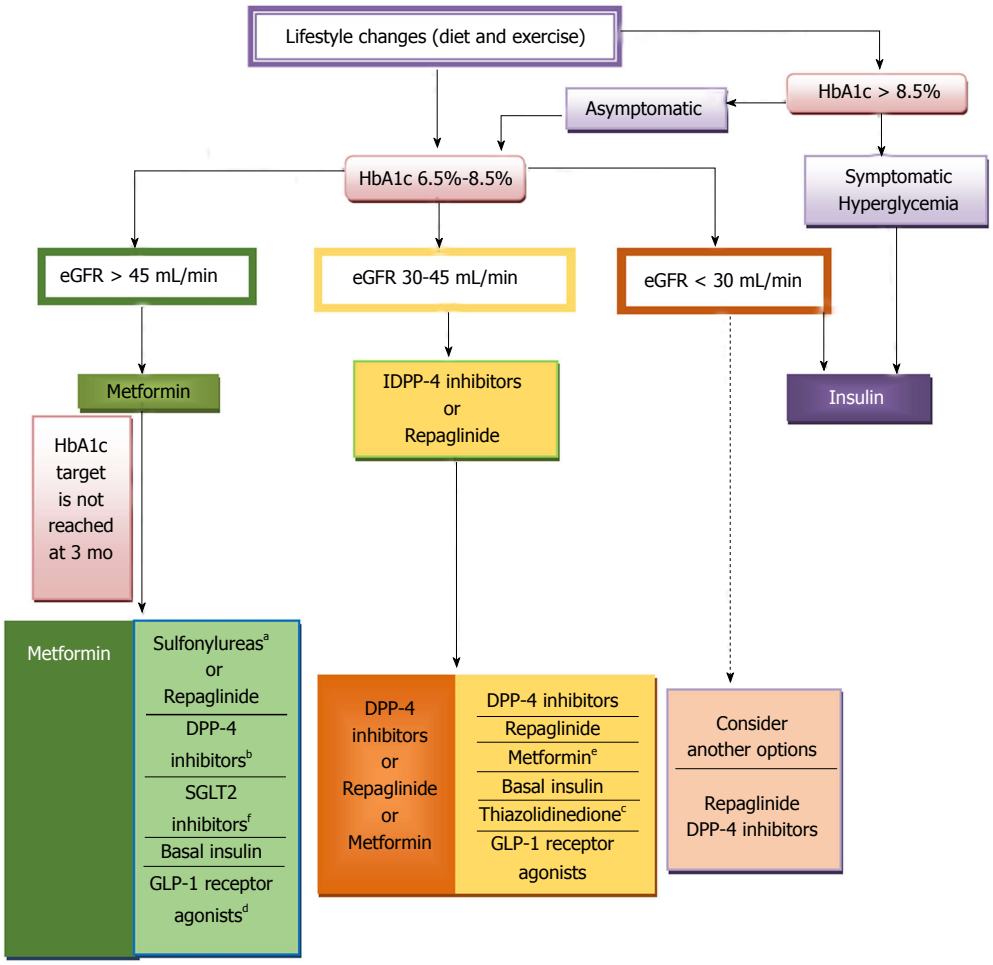

Figure 3 Therapeutic algorithm in patients with type 2 diabetes mellitus and chronic kidney disease. Adapted from Gómez-Huelgas *et al*[338]. [a]Avoid Glibenclamide. Use Gliclazide, Glipizide and Gliquidone. Use Glimepiride only if eGFR > 60 mL/min; [b]Dose adjustment, except linagliptin; [c]Monitor fluid retention; [d]Adjust doses of exenatide and lixisenatide; [e]Generally not use Metformin. Use only half the dose and monitor renal function; [f]Not recommended if eGFR < 60 mL/min. eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose co-transporter 2; DPP-4: Dypeptydil peptidase-4.

inhibitors acarbose and miglitol cannot be used if the eGFR is < 25 mL/min or the serum creatinine level is > 2 mg/dL[279,291,293,302], while voglibose can be used in all stages of CKD including haemodialysis[300,301].

Thiazolidinediones: Pioglitazone and rosiglitazone (only available in United States) are mainly metabolized in the liver and although a significant amount of active metabolites are eliminated in the urine; there is no need dose adjustment for either of these agents for patients with CKD[303]. However, both TZD cause fluid retention and increase the risk of heart failure, a problem that may be worse in patients with CKD. Although no dose adjustment in patients with CKD stages 3 to 5 is recommended[290], its use in patients with CKD should be balanced with the possibility of worsening of fluid retention and fractures, the latter particularly in patients with underlying bone disease[290,304,305].

DPP-4 inhibitors: iDPP4 are effective at lowering HbA1c in T2DM patients with moderate to severe renal impairment[304]. All iDPP4 differ in their renal excretion and therefore should be handled differently in patients with impairment renal function. Results from dedicated pharmacokinetics studies in subjects with various degrees of renal impairment suggest that the daily doses of all iDPP4 except linagliptin should be adjusted according to eGFR[305]. Several studies have demonstrated that the glucose-lowering efficacy is maintained while a good safety profile when reduced doses of these gliptins are utilized in patients with renal impairment[306-309]. On the other hand, linagliptin not require any dose adjustment in case of renal impairment, because is mainly excreted by the biliary route[310], and can be used in patients with all degrees of CKD[311]. Sitagliptin is largely excreted unchanged in the urine (87%) or *via* the feces (13%). No dose adjustment is necessary in patients with an eGFR > 50 mL/min, and can be utilized with dose reduction in patients with moderate to severe renal impairment[279,291,292,312]. The dose should be reduced by half in patients with an eGFR 30-50 mL/min, and a quarter in those with an eGFR < 30 mL/min or requiring dialysis. Around 80% of vildagliptin dose is metabolised

mostly in the kidneys into non-active metabolites which are then renally excreted (85%) or recovered in the feces (15%)[313]. Vildagliptin not need dose adjustment in patients whose eGFR is > 50 mL/min and with caution in those with ESRD. The dose should be reduced by half in patients with moderate to severe renal impairment[279,291,292]. Saxagliptin is metabolised mainly in the liver to an active metabolite that is renally excreted, with approximately 20% of a dose being recovered unchanged in the urine and 20%-50% as metabolites[314]. No dose adjustment is required for patients with an eGFR > 50 mL/min, whereas the dose should be reduced by half in patients with moderate or severe renal impairment[279,291,292]. Vildagliptin can not be utilized in those on renal replacement therapy. Linagliptin is excreted almost entirely unchanged in bile, and its elimination is essentially *via* the feces[315]. No dose adjustment is required in patients with any stage of CKD[279,291,292] including, with caution, those requiring renal replacement therapy[316,317]. Alogliptin does not suffer appreciable metabolism and around 80% is eliminated unchanged in urine[318]. No dose adjustment is required for patients with an eGFR > 50 mL/min. Alogliptin dose adjustments are recommended for patients with moderate to severe renal impairment, including those with ESRD requiring dialysis. The dose should be reduced by half in patients with an eGFR 30-50 mL/min, and a quarter in patients with an eGFR < 30 mL/min or ESRD[279].

Sodium-glucose co-transporter 2 inhibitors: iSGLT2 decrease plasma glucose concentration by inhibiting the reabsorption of glucose by the kidney, which in turn, is a function of plasma glucose concentration and GFR. Because these agents rely on GFR to increase urinary glucose excretion, they are expected to have a decreased effect as kidney function declines. Studies examining the efficacy of iSGLT2 inhibition in patients with diabetes have been reported for a number of iSGLT2 including canagliflozin[319], dapagliflozin[320], empaglifozin[321] and ipragliflozin[322]. As expected, the efficacy of iSGLT2 decreases as kidneys function decreases[320-322]. Although renal function does not seem to be affected[141], its use in patients with moderate to severe CKD is not recommended. Dapagliflozin is not recommended if the eGFR is < 60 mL/min. In patients with an eGFR < 60 mL/min., canagliflozin and empagliflozin should not be initiated, but they may be continued in patients already taking the medications. Patients with an eGFR of 45-60 mL/min should be of the lower doses once a day, and both medications are contraindicated in patients with an eGFR < 45 mL/min, or on dialysis[139].

RA-GLP1: Due to the effect of these agents on gastric emptying, side effects are mainly gastrointestinal: Nausea, vomiting and diarrhoea. These gastrointestinal side effects with recurrent vomiting will lead to dehydration and secondary acute renal failure[323]. Exenatide is extensively renally eliminated by glomerular filtration and undergoes degradation by the kidneys to small, inactive peptide fragments[324]. There is reduced clearance in people with renal impairment[325]. Exenatide can be utilized in patients with and eGFR > 50 mL/min, whereas cannot be used in patients with an eGFR < 30 mL/min. In subjects with an eGFR of 30-60 mL/min, exenatide should only be employed with great caution and a lower doses[279,291,302]. Liraglutide is metabolised in a similar manner to large proteins, and its shows no reduced clearance in patients with renal impairment, and undergoes only minimal renal excretion[326]. No dose adjustment is required in subjects with an eGFR > 30 mL/min. Limited data are available in patients with an eGFR < 30 mL/min and ESRD, and should not be used in these populations[326]. As a peptide, lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation. No dose adjustment is recommended for patients with an eGFR > 50 mL/min, but as there is limited therapeutic experience in patients with an eGFR 30-50 mL/min, lixisenatide should be utilized with caution and is contraindicated in those with an eGFR < 30 mL/min and with ESRD[327]. Albiglutide is a protein, so the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes. No dose adjustment is necessary in subjects with an eGFR > 30 mL/min. Limited data are available in subjects with an eGFR < 30 mL/min and should be used with caution in these populations[328]. Finally, dulaglutide is presumed to be degraded into its component amino acids by general protein pathways. No dose adjustment is recommended in subjects with renal impairment including ESRD. Limited data are available in patients with an eGFR < 30 mL/min, and should be employed with caution[329].

Insulin: Insulin is generally considered to be safe in patients with a reduced kidney function. Because of their low levels of degradation, insulin prolongs its half life when there is an impairment in kidney function[330]. As a result the risk of hypoglycaemic events is 5 times higher than in subjects without impairment renal function[331]. Almost 50% of circulating insulin is cleared by the kidney *via* glomerular filtration and subsequent luminal reabsorption of insulin by proximal tubular cells by means of endocytosis, or *via* diffusion of insulin from peritubular capillaries and subsequent binding of insulin to the contraluminal membranes of tubular cells. In insulin-treated T2DM patients, insulin doses should be reduced by 25% when the eGFR is between 10-50 mL/min, and by 50% when the eGFR is < 10 mL/min[332,333]. As for human insulin, the pharmacokinetic/pharmacodynamic profiles for insulin analogs may be influenced by many variables including renal function, although the available data are rather scarce[334]. Reduction of initial glargine/glulisine insulin weight-based dosing in hospitalized patients with T2DM and renal impairment reduced the frequency

of hypoglycaemia by 50% without compromising the control of hyperglycaemia[335]. Short-acting insulin analog can also be utilized in haemodialysis patients with T2DM[336].

Figure 3 shows the therapeutic algorithm for the treatment of patients with T2DM and CKD, proposed by the Spanish Working Group, sponsored by several scientific societies[337].

BARIATRIC SURGERY

Bariatric surgery could be an alternative in the treatment of obesity. Candidates for bariatric surgery are patients with a morbid obesity or those with a BMI > 35 kg/m^2 who also have co-morbidities, such as hypertension, T2DM or obstructive sleep apnoea. After this surgery, it was observed a metabolic response leading to decrease blood glucose with improvements or remission of diabetes. Moreover, bariatric surgery also improves the metabolic status, improving lipid profile and hypertension, thus decreasing cardiovascular risk[338].

The improvement in glycaemic control, has been observed before the achievement of clinically significant weight loss. Although there are no consistent theories to explain the early improvement in T2DM after surgery, it seems a direct consequence of gastrointestinal anatomy restructuring that produces hormonal change and decreases food intake with an acute negative calorie balance[339]. This supports the idea that "metabolic surgery" is a definition more appropriate, and it refers a bariatric surgery in patients with less grade obesity than those who are traditionally eligible for bariatric surgery[338]. Despite this, it is necessary more investigation for known entirely the relationship between metabolic effects of bariatric surgery in overweight and in patients with obesity class I.

THE FUTURE IN THE TREATMENT OF DIABETES

Unfortunately, all anti-diabetic agents have adverse effects, and are expensive. Therefore, the investigation of novel antidiabetic regimens, with less adverse effects and cheaper, is a major challenge for researchers.

Polyphenols

Natural products containing high polyphenol levels as blackberries, red grapes, apricots, eggplant, coffee, cocoa and green tea can regulate glucose metabolism through different paths, such as restoring beta-cell integrity, enhancing insulin releasing activity, and increasing cellular glucose uptake, which can improve insulin resistance[340].

Smart insulin patch

A new smart insulin patch has been created. It is a thin square covered with more than 100 tiny needles. The patch made of biocompatible materials works fast and it's easy to use. The patch consists of small painless needles that are packed together with insulin and glucose-sensitive enzymes in microscopic storage units. The patch releases these enzymes when blood glucose increases. In a mouse model, patch administration showed reduced glucose levels up to 9 h[341]. It is suggested that the patch could have a longer effect in diabetic humans since humans are more sensitive to insulin than mice.

Dual-acting peptide

GLP1 and GIP are the two main incretin hormones that are released from the intestine in response to food intake. Both hormones stimulate glucose-dependent insulin secretion. Evidence from animal studies suggests that anti-obesity efficacy of GLP1 can be enhanced by co-administration with the incretin hormone GIP. Finan *et al*[342] showed that an acylated version of GLP1 and GIP dual agonist, reduced weight (-18.8% *vs* -8.8%, $P < 0.001$), food intake ($P < 0.05$), fat mass ($P < 0.001$) and blood glucose ($P < 0.05$), compared to liraglutide. Also showed increases in plasma insulin and C-peptide more pronounced that liraglutide ($P < 0.001$ for both). No differences in improved glycaemic control between these co-agonists and liraglutide were found. In T2DM patients they found a dose-dependent reductions of HbA1c, being -0.53% in patients treated with 4 mg of the dual agonist, and -1.11% in those treated with 30 mg, compared with placebo (-0.16%). The pharmacokinetics and pharmacodynamics results of co-activation of GLP1 and GIP receptors[343] are considered as a promising new strategy for the treatment of obese T2DM patients, to prolong the activity of GLP1 and GIP dual agonists, and for the future development of a possible once-weekly GLP-1 and GIP dual agonists drug candidate for the treatment of T2DM.

GLP1 and Glucagon receptor dual agonism: Glucagon and GLP1 have distinct receptors that are also structurally related[344]. Glucagon stimulates gluconeogenesis and glycogenolysis in the liver, raising blood glucose levels; while GLP1 reduce blood glucose levels by increasing insulin synthesis and secretion in the pancreas[345]. Administration of oxyntomodulin, a GLP1 receptor/glucagon receptor dual agonist peptide, to rodents[346-348] and humans[349,350], resulted in a improvement of glucose metabolism by decreasing food intake and body weight, and increasing energy expenditure, more pronounced than those reported by GLP1. Moreover, weekly administration of PEGylated peptides reduced adiposity and improved glucose tolerance in diet-induced obese mice[351], and sustained GLP1/glucagon dual agonism reverses obesity in diet-induce obese mice[352]. These co-agonist compounds also normalized glucagon, glucose and lipid metabolism and reduced liver steatosis, and is a novel therapeutic approach to the treatment of obesity in patients with

T2DM.

GLP1 receptor agonist and Glucagon receptor antagonism activity: GLP1/Glucagon hybrid peptides, a dual acting peptide that bind both receptors, for diabetes (DAPD) have been reported previously[344], and more recently have been identified *in vitro*[353]. Administration of PEGylated DAPD in mice, showed a decrease in blood glucose by increasing insulin secretion GLP1-induced, and a rise in fasting glucagon levels following a glucagon challenge[354]. Moreover, unlike RA-GLP1, does not inhibit gastrointestinal motility and has not adverse events at this level.

Basal insulin analogs with glucagon-like peptide-1 mimetics

The combination of GLP1 mimetics with basal insulin reduced the risk of hypoglycaemia and weight gain induced for intensive insulin regimens in T2DM patients. Preliminary evidence suggests that the addition of a basal insulin to a GLP1 mimetic with or without oral therapy, provide improvements in basal and postprandial glucose control, with less weight gain, reduced risk of hypoglycaemia and increased satisfaction[188-190,355-358]. Data from the DUAL Ⅰ extension (insulin-naïve patients not controlled with oral hypoglycaemic agents) and DUAL Ⅱ (patients not controlled on basal insulin plus oral hypoglycaemic agents) randomized trials, the novel fixed combination of insulin degludec and liraglutide (IDegLira), effectively lowered HbA1c across a range of measures, implying suitability for patients with either early or advanced T2DM[359]. LixiLan is a new once-daily single injection fixed-ratio combination of lixisenatide, and insulin glargine. Results from the Lixilan-L trial, showed that LixiLan successfully met the primary study endpoint of demonstrating a statistically superior reduction in HbA1c compared with insulin glargine[360].

G protein-coupled receptor 119

G protein-coupled receptor 119 (GPR119) agonists is a G protein-coupled receptor that is expressed predominantly in the pancreas and gastrointestinal tract in rodents and humans, as well as in the brain in rodents[361]. Activation of the receptor showed a reduction in food intake and body weight gain in rats[361]. GPR119 has also been shown to regulate incretin and insulinsecretion[362-364]. New agents acting on this receptor have been suggested as novel treatments for obesity and diabetes[361,363,365].

It is worth pointing out the potential advantages that could be obtained by the co-administration of a GPR119 agonist and a iDPP4. The role of these additional hormonal agents will required to clarify in the further study[366].

Oral RA-GLP1

Currently, RA-GLP1s are available only as injectables, either once daily or once weekly. Semaglutide is a long-acting RA-GLP1 that is also being developed as a once-weekly injectable. An oral semaglutide version leading to higher solubility and protection from enzymatic degradation is also being developed.

The phase 2 study[367] enrolled 632 adults with T2DM of 6 to 7 years duration, managed with lifestyle with or without metformin, and HbA1c 7.0% to 9.5% (mean, 7.9%). They were randomized to oral semaglutide in doses of 2.5, 5, 10, 20 or 40 mg once daily, or to placebo, or to open-label injected once-weekly 1.0-mg semaglutide. Patients started at 2.5 or 5 mg once daily and the higher-dose groups were titrated up at 4-wk intervals. The primary endpoint was change in HbA1c from baseline to week 26.

At 26 wk, mean HbA1c decreased dose-dependently with oral semaglutide, with drops ranging from 0.7% with 2.5 mg to 1.9% with 40 mg. Subcutaneous once-weekly semaglutide also produced a 1.9% drop in HbA1c, while the placebo group experienced a decrease of only 0.3% (P = 0.07 for 2.5 mg *vs* placebo, P < 0.0001 for other doses). For all the groups taking 5-mg oral semaglutide or higher doses, more than 80% of the patients achieved HbA1c values less than 7%, and the groups treated with 10-mg dose or more achieved mean HbA1c less than 6.5%. Fasting plasma glucose also dropped significantly, from a baseline of 170 mg/dL, with reductions ranging from 17 mg/dL with 2.5 mg to 51 mg/dL for the other oral doses (P = 0.08 for 2.5 mg, P < 0.0001 for other doses) and a reduction of 56 mg/dL with 1.0-mg subcutaneous semaglutide *vs* 1 mg/dL with placebo.

The proportion of patients achieving 5% or more weight loss was 21% to 71% in the oral group and 66% in subcutaneous group, compared with 13% in the placebo group.

None of the adverse events were considered serious and all were reported as mild to moderate in severity. Increases in lipase levels were greater in the oral and subcutaneous semaglutide groups, compared with placebo.

Based on these data, oral semaglutide is now being studied in a large phase 3 trial[368].

Oral insulin

Oral administration of insulin is a novel treatment to improve glycaemic control in patients with T2DM. Oral insulin has a more physiological action than parenteral insulin. Due to its first pass through the liver, it reduces glycogenolysis, hepatic glucose production, and the risk of hypoglycaemia, compared with parenteral insulin. Currently, the data available in human trials suggest that could be a novel approach to the treatment of diabetes[369,370].

There are several oral insulins in development: Short-acting insulins as ORMD-0801 (Oramed) and Capsulin (Diabetology) in phase 2 studies, and the IN-105 (Biocon) in phase 3 studies; and basal insulins,

such as the OI287GT (NN1956) (NovoNordisk).

Dual inhibition of SGLT1 and SGLT2

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 with approximately 20-fold selectivity for SGLT2 over SGLT1[371]. Animal pharmacology studies showed that sotagliflozin produced increased urinary glucose excretion, delivery of glucose to the caecum, increased postprandial GLP1 and peptide YY release, that were related with significant reductions in postprandial glucose[372,373]. Sotagliflozin was evaluated in patients with T2DM not controlled with metformin[372]. Sotagliflozin reduced fasting plasma glucose and HbA1c with a modest urinary glucose excretion, compared with selective iSGLT2. The high glycaemic efficacy observed with only modest urinary glucose excretion suggested that clinically relevant gastrointestinal SGLT1 inhibition was present. Phase 1 and phase 2 studies have identified special opportunities for synergy with iDPP-4 for treatment of patients with T2DM and renal impairment.

Other treatments

Technosphere insulin, a new inhaled insulin represent an alternative to bolus insulin injections, but can be used concomitantly with basal insulin injections. Its hypoglycaemic effect is less than the rapid-acting insulin, but has less hypoglycaemias[374]. Major adverse effects are respiratory, with cough being the most prominent, and there is a small decrease in the forced expiratory volume in 1 s (FEV1) with technosphere insulin, consistent, no progressive, and reversible; so that patients must receive pulmonary function test periodically throughout therapy. Should be utilized with caution in patients who smoke and is contraindicated in patients with chronic lung disease.

New chitosan formulations of xanthine derivatives (CS-6, CS-7) have been synthesized as antidiabetic and antioxidant treatments. Formulations of chitosan 6 (CS-6) have shown to reduce blood glucose levels by 59.3%, with a recorded 4.53% HbA1c level[375]. These effects were more intense than the induced by pioglitazone (114.5 mg/dL *vs* 148.5 mg/dL), when used as standard antidiabetic medication. These results have shown the potential application of chitosan formulations of Xanthine 6 derivates (CS-6) in the treatment of diabetes mellitus.

Recent studies have shown the dynamic role of zinc, an insulin mimetic, as a "cellular second messenger" in glucose homeostasis and in the control of insulin signaling[376]. Synthesis, secretion and insulin action are dependent on zinc and transporters. This suggests that zinc plays a role, previously not identified, where changes in the state of zinc over time can affect the activity of insulin. This is a novel area of investigation, and introduces a new class of useful drugs for diabetes pharmacotherapy.

Imeglimin is the first of the family of agents called "glimins" and, more specifically, is a tetrahydrotriazene compound[377]. Laboratory studies[377,378] have shown that acts on impaired glucose uptake by muscle tissue, excessive hepatic gluconeogenesis, and increased apoptosis of beta cells. Imeglimin is still in development and human studies are limited. The few human studies recently published[377,379-381] show that reduces HbA1c and fasting glucose similar to sitagliptin and metformin, with a low incidence of side effects, especially hypoglycaemia. Currently, there is an ongoing trial that evaluated the safety and efficacy of imeglimin with insulin therapy or compared directly with insulin in patients newly diagnosed or treated with oral monotherapy, whose results have not yet been published[382]. Imeglimin seems to be a promising antidiabetic agent as monotherapy in the treatment of T2DM.

Recent studies reported a possible role of the G protein coupled receptor 40 (GPR40), also known as FFAR 1, in the regulation of beta-cell function[383]. It was reported that chronic treatment of male zucker diabetic fatty (ZDF) rats (insulin resistant model with elevated blood glucose and FFAs levels) with CNX-011-67 (GPR40 agonist) increased insulin secretion, decreased blood glucose and reduced beta-cell apoptosis without affecting body weight[384]. From this study data it appears that CNX-011-67 could have the potential to provide good and durable glycaemic control in T2DM patients. Another study provided evidence that activation of GPR40 with CNX-011-67 stimulates glucose metabolism, improve glucose responsiveness and enhances insulin secretion, with the hope that pharmacological activation of GPR40 will prove beneficial for the treatment of T2DM[384]. TAK-875, a novel highly selective, orally bioavailable GPR40 agonist, significantly improved glycaemic control in patients with T2DM with a minimum risk of hypoglycaemia. The outcomes show that activation of FFAR1 is a viable therapeutic target for the treatment of T2DM[385]. According to current data it can be appreciated that beta-cell failure could be delayed or prevented by attaining and maintaining good glycaemic control. It is theoretically possible to inhibit multiple mechanisms by blocking the pathways leading to beta-cell apoptosis, and this is a challenge for the future.

Finally, *in vivo* studies, administration of hot water extracts of Salacia chinensis to diet-fed KK-A^{y} mice, resulted in a significant reduction in the basal and postprandial blood glucose and HbA1c levels; with an improvement of glucose tolerance[386]. The active components, salacinol, kotalanol, and neokotalanol inhibited human α-glucosidases as potently as they inhibited rat small intestinal α-glucosidase. The results suggest that these sulfoniums can be good candidates as new type of anti-diabetic agents.

CONCLUSION

While lifestyle modifications and metformin are the cornerstone of the initial management of T2DM, there is an increasing array of second and third-line pharma-

cological agents for this condition. At present there are different families of oral and injectable drugs, available for the treatment of T2DM. These include sulfonylureas, meglitinides, insulin, TZD and alpha-glucosidase inhibitors, and recently with the addition of RA-GLP1 receptor agonists, iDPP4 and iSGLT2. Moreover, insulin analogues that better simulate endogenous insulin secretion have been developed. Metformin remains the first choice of treatment for most patients. Other alternative or second-line treatment options should be individualized taking into consideration patient characteristics as degree of hyperglycaemia, presence of co-morbidities, and patient preference and ability to access treatments; and properties of the treatment such effectiveness and durability of lowering blood glucose, risk of hypoglycaemia, effectiveness in reducing diabetes complications, effect on body weight, side effects and contraindications. Although it does not appear that in the near future cure diabetes, novel safety and effective agents that will improve the quality of life of T2DM patients, are developing.

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REVIEW

Evidence for current diagnostic criteria of diabetes mellitus

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Abstract

Diabetes mellitus is a non-communicable metabolic derangement afflicting several millions of individuals globally. It is associated with several micro and macrovascular complications and is also a leading cause of mortality. The unresolved issue is that of definition of the diagnostic threshold for diabetes. The World Health Organization and the American Diabetes Association (ADA) have laid down several diagnostic criteria for diagnosing diabetes and prediabetes based on the accumulating body of evidence.This review has attempted to analyse the scientific evidence supporting the justification of these differing criteria. The evidence for diagnosing diabetes is strong, and there is a concordance between the two professional bodies. The controversy arises when describing the normal lower limit of fasting plasma glucose (FPG) with little evidence favouring the reduction of the FPG by the ADA. Several studies have also shown the development of complications specific for diabetes in patients with prediabetes as defined by the current criteria though there is a significant overlap of such prevalence in individuals with normoglycemia. Large multinational longitudinal prospective studies involving subjects without diabetes and retinopathy at baseline will ideally help identify the threshold of glycemic measurements for future development of diabetes and its complications.

Key words: Diabetes; Prediabetes; Post glucose; Microvascular complications; Macrovascular complications

Core tip: The diagnostic criteria for diabetes and prediabetes have evolved along the timeline taking into account new evidences which had developed. The major professional bodies have converged on to a consensus in developing the different thresholds for diagnosis of diabetes and associated states. Nevertheless,controversy remains on certain issues. There

is need to review the evolution of these criteria, the logistics behind their adoption and their association with different complications.

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INTRODUCTION

Diabetes mellitus (DM) is a classic non-communicable disease that contributes to morbidity, mortality and poor quality of life apart from imposing economic burden on the health care system. The prevalence of type 2 DM is rising steadfast at an alarming rate and is estimated to affect 592 million individuals globally by the year 2035[1]. The International Diabetes Federation projections of the prevalence of prediabetes are expected to reach 471 million by 2035[1]. It is essential to make an early diagnosis and begin intervention to avoid complications of DM. But, defining the diagnostic threshold for diabetes and prediabetes has been a matter of intense debate. In this regard, several professional bodies have published differing diagnostic criteria over the last few decades. Below, is a review of the evolution of various diagnostic criteria and their validity.

EVOLUTION OF DIAGNOSTIC CRITERIA FOR DIABETES

In ancient times, DM was diagnosed by tasting urine. Then the diagnosis was made by estimation of glucose in urine.But urine glycosuria did not correlate with glucose level in blood and was replaced by estimation of plasma glucose.

World Health Organization criteria (1965)

The World Health Organization (WHO) in 1965 proposed the first widely accepted laboratory standard for diagnosing DM (Table 1). The committee recommended diagnosing DM in persons under the age of 45 years if 2 h venous plasma glucose was ⩾ 7.22 mmol/L after loading with oral glucose of 50 or 100 g[2]. In persons aged more than 45 years, the committee considered that other clinical data should be the main guide to the diagnosis. Borderline state was defined if 2 h plasma glucose level was between 6.11 to 7.17 mmol/L.

National Diabetes Data Group criteria (1979)

The National Diabetes Data Group (NDDG) in 1979 proposed new diagnostic criteria for DM[3]. It was based on the bimodal distribution of plasma glucose observed in Pima Indians and Nauruan population and the risk of progression to DM and its complications[4,5]. A subject was diagnosed as having DM if fasting plasma glucose (FPG) was ⩾ 7.78 mmol/L and/or 2-h plasma glucose (2-h PG) after 75 g of glucose was ⩾ 11.11 mmol/L.

A study on Pima Indians revealed that the 2-h PG level differentiated those with DM from those without[4]. Subjects fall into two groups, one with a distribution of 2-h PG levels below 11.11 mmol/L, and the other with a distribution above 13.33 mmol/L. Diabetic retinopathy was mainly confined to the second group, *i.e.*, in subjects whose 2-h PG level ⩾ 13.33 mmol/L and this value divided the subjects with diabetes from nondiabetics. This bimodal distribution was further confirmed in Nauruan population[5]. Similar bimodal distribution also exists for FPG, where the glycemic threshold of about 7.78 mmol/L divides the two groups. Later, the bimodal glycemic distribution was reconfirmed from other populations with a high prevalence of DM like Mexican Americans[6], Pacific Islanders[7], South African Indians[8], Egyptians[9], Malaysians[10] and Americans in the United States[11]. However, for some populations, no such bimodality could be documented[12].

With accumulating evidence from further studies, it was recognized that several individuals had 2-h PG levels that were intermediate between the normal and diabetic range. This group of individuals had 1%-5% risk of progression to DM per year though the majority continued to remain in this state and a few reverted to normalcy. It was also noted that there was an increased prevalence of atherosclerotic disease and electrocardiographic abnormalities and death in this population. This provided a window of opportunity to identify such individuals to intervene early and prevent progression to DM and its complications. To lay emphasis on this, the terminology "impaired glucose tolerance" (IGT) was first introduced by the NDDG of the National Institute of Health, United States. It was defined as a state of having venous FPG level of less than 7.8 mmol/L and a 2-h PG oral glucose tolerance test (OGTT) value between 7.8 mmol/L and 11.1 mmol/L[3].

This group also aimed to standardize the protocol for OGTT internationally and recommended using 75 g of anhydrous glucose load for testing in nonpregnant adults. This was based on the observation that 50-g dose was not adequate in many individuals to identify IGT detected using the larger dose. Also, 100-g dose resulted in significant nausea in several study subjects. In subjects without diabetes it was reported that 50 g or 100 g result in aproximaltely similar plasma glucose levels, the only difference was that 2 h PG was 0.83 mmol/L higher for 100 g as compared to 50 g oral glucose load[13,14]. Also there were no significant differences between 75- and 100-g doses. But in subjects with IGT there was higher difference (up to 2.78 mmol/L) in 2-h PG value between the 50 and 100 g oral glucose[3].

WHO criteria (1980 and 1985)

The WHO technical recommendation released in 1980

Table 1 Evolution of diagnostic criteria of diabetes mellitus

	WHO 1965	WHO 1980	WHO 1985	ADA1997 WHO 1999	ADA 2003	IEC 2009 ADA 2010 WHO 2011
IFG	Not defined	Not defined	Not defined	Fasting ⩾ 6.11 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L	Fasting ⩾ 5.5 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L	Fasting ⩾ 5.5 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L or HbA1c (5.7%-6.4%)
IGT	Post glucose 6.11-7.1 mmol/L	Fasting < 8 mmol/L and/or post glucose ⩾ 8 to < 11.1 mmol/L	Fasting < 7.8 mmol/L and/or post glucose ⩾ 7.8 to < 11.1 mol/L	Fasting (if measured) < 7 mmol/L and post glucose ⩾ 7.8 to 11.1 mmol/L	Fasting (if measured) < 7 mmol/L and post glucose 7.8 to 11.1 mmol/L	Fasting (if measured) < 7 mmol/L and post glucose 7.8 to 11.1 mmol/L or HbA1c (5.7%-6.4%)
DM	Post glucose ⩾ 7.22 mmol/L	Fasting ⩾ 8 mmol/L and/or post glucose ⩾ 11.1 mmol/L	Fasting ⩾ 7.8 mmol/L and/or post glucose ⩾ 11.1 mmol/L	Fasting ⩾ 7 mmol/L and/or post glucose ⩾ 11.1 mmol/L	Fasting ⩾ 7 mmol/L and/or post glucose ⩾ 11.1 mmol/L	Fasting ⩾ 7 mmol/L or Post glucose ⩾ 11.1 mmol/L and/or HbA1c ⩾ 6.5%

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; DM: Diabetes mellitus; IEC: International Expert Committee; ADA: American Diabetes Association; WHO: World Health Organization; HbA1c: Glycated hemoglobin.

modified the criteria for diagnosing DM (Table 1). A venous FPG value above 8 mmol/L and a post glucose load 2-h PG value above 11 mmol/L were considered diagnostic of DM. This 2-h PG value was chosen based on observations that specific complications of DM rarely developed below this threshold. The term "IGT" suggested by the NDDG was also endorsed by WHO and became a part of the recommendation[15]. This was further slightly modified in the subsequent recommendations in 1985 and fasting and 2-h post glucose load venous plasma glucose thresholds were redefined as 7.8 mmol/L and 11.1 mmol/L respectively (Table 1)[16].

American Diabetes Association criteria (1997) and WHO criteria (1999)

In 1997, the American Diabetes Association (ADA) lowered the threshold for FPG from 7.8 to 7.0 mmol/L and the 2-h post glucose load value was retained (Table 1)[17]. Impaired fasting glucose (IFG) was defined as FPG ⩾ 6.1 mmol/L and < 7.0 mmol/L (Table 1). WHO adopted these criteria for the diagnosis of diabetes and prediabetes in 1999. In the second National Health and Nutrition Examination Survey (NHANES-Ⅱ), only 26% of people with newly diagnosed DM by 1985 WHO had FPG ⩾ 7.8 mmol/L, whereas 97% had 2-h PG ⩾ 11.1 mmol/L[18]. Other studies also reported that as many as 80% of DM cases discovered in population screening by OGTT have FPG < 7.8 mmol/L[19-25]. Thus, the cutpoint of FPG > 7.8 mmol/L defined a greater degree of hyperglycemia than did the cutpoint of 2-h PG > 11.1 mmol/L. Thus, FPG appeared to be an insensitive test in population screening for undiagnosed DM.

This revision of the diagnostic criteria for the FPG from 7.8 to 7.0 mmol/L was based on the assumption that the threshold of the FPG and 2-h PG should identify similar conditions. In Pima Indians[26], Egyptians[9] and NHANES-Ⅲ, both FPG and 2-h PG were strongly associated with retinopathy. The cutpoint for the 2-h PG was justified largely because of the dramatic increase in the prevalence of retinopathy approximately around that point. The equivalent cutpoint of FPG for 2-h PG level predicting retinopathy was computed in population studies of the Pima Indians, Egyptians, Pacific population, and NHANES Ⅲ participants.

ADA criteria (2003)

A controversial change was brought out in the 2003 ADA guidelines, and it was the reduction in the cut-off point for defining the upper limit of FPG (Table 1). Based on four population-based epidemiological studies, the ideal cut-off point was shown to fall between 5.22-5.72 mmol/L and based on this data, an arbitrary cut-off of 5.55 mmol/L was chosen as the new threshold[27]. The lower threshold value of IFG was reduced from 6.11 to 5.55 mmol/L.

The phases of IFG and IGT represent metabolic states intermediate between normal glucose homeostasis and diabetic hyperglycaemia. The physiological basis of IFG and IGT are different. IFG is associated with insulin resistance at liver while IGT is associated with peripheral insulin resistance, at the level of skeletal muscle. The rationale for establishing the intermediate categories of impaired glucose regulation was based on their ability to predict future diabetes and its complications. The idea behind selecting the lower limit of IFG would be the identification of a threshold of FPG at which the risk of development of DM and complication or metabolic rises sharply. Data from Mauritius[28] and DECODE study[29] indicate that such a threshold of FPG does not exist for cardiovascular risk factors, all-cause mortality, or future DM. This criterion was based on

receiver operating characteristics (ROC) curve analyses of Pima Indian, Mauritius, San Antonio and Hoorn study data, which identified the baseline FPG levels, which maximised sensitivity and specificity for predicting DM over a 5-year period[25]. The ROC curve analyses indicated that a cut-point of 5.4-5.5 mmol/L gives the best combination of sensitivity and specificity for predicting future DM.

ADA criteria (2010) and WHO criteria (2011)

International Expert Committee (IEC 2009)[30], ADA in 2010 and WHO in 2011 recommended a glycated hemoglobin (HbA1c) level of ⩾ 6.5% as a diagnostic cut-off for DM (Table 1). HbA1c level reflects the average plasma glucose level over preceding three months. HbA1c is more convient than glucose because it does not require fasting samples and is also not affected by recent changes in diet or activity. Another limitation of plasma glucose assay is lack of consistent accuracy of assay[31]. HbA1c has a greater analytic stability and less day-to-day variability in comparison to plasma glucose[32]. Selvin *et al*[33] evaluated the variabilities of glycemic measurement and found that 2-h PG levels [within-person coefficient of variation (CV), 16.7%; 95%CI: 15.0-18.3] and FPG (CV, 5.7%; 95%CI: 5.3-6.1) had substantially more variability compared with HbA1c (CV, 3.6%; 95%CI: 3.2-4.0) levels.

HBA1C *VS* GLUCOSE CUTPOINTS FOR DIAGNOSIS OF DM

Lorenzo *et al*[34] compared 1999 WHO (2-h PG ⩾ 11.11 mmol/L) and 2003 ADA criteria (FPG ⩾ 7 mmol/L) with an HbA1c of ⩾ 6.5%. It was found that sensivity of HbA1c is poorer than plasma glucose because HbA1c diagnosed 5.2% of subjects as having diabetes compared to FPG (7.1%) and the 2-h PG (15.4%). Kramer *et al*[35] reported the sensitivity and specificity of HbA1c cutoff of 6.5% were 44% and 79% respectively based on the Rancho Bernardo Study. According to the ADA criteria, for this given HbA1c cut point of 6.5%, 85% of participants were classified as nondiabetic. Olson *et al*[36] compared HbA1c and standard OGTT for diagnosis of DM in three datasets from the prospective Screening for IGT study (n = 1581), NHANES-Ⅲ (n = 2014), and NHANES 2005-2006 (n = 1111) and reported that HbA1c criterion failed to recognize upto 70% of cases of DM. In conclusion, from above studies, HbA1c had the least sensitivity for diagnosis of DM in comparison to FPG and 2-h PG. Several studies have shown that HbA1c levels, as the plasma glucose levels, can predict the development of future DM[37,38].

A limitation of HbA1c is that it is affected by red blood cell disorders[39]. Another limitation of HbA1c is that its levels depend on genetic factors[40,41]. It also suffers from analytic imprecision if methods other than high-performance liquid chromatography is used for estimation and if such tests are not standardized. Measurement of HbA1c is currently well standardized with the adaptation of "national glycohemoglobin standardization program" protocols.

OPTIMAL THRESHOLD OF THE HBA1C FOR RETINOPATHY

The most important question is how well HbA1c predicts retinopathy.IEC suggested a cutoff of the HbA1c of 6.5% for the diagnosis of DM because it was presumed that diabetic retinopathy sharply increased above this level. Unfortunately, most of the studies are cross-sectional and only a few prospective studies looked at the relationship between HbA1c and retinopathy (Table 2). Longitudinal prospective studies with subjects without DM and retinopathy at baseline will ideally give the association of HbA1c with retinopathy.

CROSS-SECTIONAL STUDIES OF HBA1C FOR RETINOPATHY PREDICTION

Colagiuri *et al*[42] analysed the pooled data of nine studies and find that diabetes-specific retinopathy (after exclusion of mild retinopathy) was observed over the HbA1c range of 6.3% to 6.7% based on vignitile distribution and 6.4% by ROC analysis. He concluded that HbA1c ⩾ 6.5% is a suitable alternative diagnostic criterion for DM. In the Australian Diabetes Obesity and Lifestyle study (AusDiab), retinopathy was assessed in 2182 participants aged ⩾ 25 years. DM was not excluded in this study. The thresholds for increasing the prevalence of retinopathy was 6.1% for HbA1c[43]. Sabanayagam *et al*[44] examined the relationship of HbA1c to retinopathy in population-based sample of 3190 Malay adults aged 40-80 years in Singapore. HbA1c cut-off point of 6.6% detected mild retinopathy [87.0% sensitivity, 77.1% specificity and area under curve (AUC) 0.899] and 7.0% detected moderate retinopathy (82.9% sensitivity, 82.3% specificity and AUC 0.904). The prevalence of mild and moderate retinopathy was < 1% below the optimal cut-off points. Xin *et al*[45] in Chinese population and Cho *et al*[46] in South Korean population found a threshold of 6.5% for detection of retinopathy. In ARIC study[47], lower AUC was found (0.561 for any retinopathy, 0.543 for mild retinopathy and 0.658 for moderate) to severe retinopathy. These studies show that though there is an association between HbA1c and retinopathy, an optimal threshold could not be established.

LONGITUDINAL STUDIES OF HBA1C FOR RETINOPATHY PREDICTION

Tsugawa *et al*[48] analyzed longitudinal data of 19897 Japanese adults who underwent a health checkup in 2006 and were followed up three years later. Logistic

Table 2 Longitudinal studies assessing the glycated hemoglobin thresholds for retinopathy

Ref.	Study population characteristics	Assessment of retinopathy	Method of determining cutoff	Cut off
Tsugawa *et al*[48]	3 yr follow-up; number = 19987 Japanese subjects; age ⩾ 21 yr; diabetes not excluded	Nonmydriatic 45° retinal photograph	Test for nonlinearity in multivariate logistic regression models with restricted cubicspline Multivariate logistic regression with categories of HbA1c as independent variable	Possible threshold at HbA1c levels between 6% and 7% 6.5%-6.9%
van Leiden *et al*[49] Hoorn study	7.9-11.0 yr follow-up; number = 233; age 50-74 yr; analyses in total study group and in subjects without diabetes	Ophthalmoscopy and fundus photography	Logistic model with categories of HbA1c (adjusted for age, sex, hypertension, glucose metabolism category)	No threshold found

HbA1c: Glycated hemoglobin.

regression analysis found that individuals with HbA1c levels of 6.5%-6.9% were at significantly higher risk of developing retinopathy at 3 years compared with those with HbA1c levels of 5.0%-5.4% [adjusted odds ratio, 2.35 (95%CI: 1.08-5.11)]. The incidence of retinopathy was determined in 233 individuals, aged 50 to 74 years, by ophthalmoscopy and fundus photography at baseline and after an average follow-up of 9.4 years in the Hoorn study[49]. Incidence of retinopathy was found to be significantly increased for HbA1c ranging between 5.8%-13.1% compared to HbA1c between 4.3%-5.2% but no optimal thresold of HbA1c was determined as the number of subjects in the study was not adequate.

Thresholds of HbA1c for retinopathy differ widely in the studies because of several reasons. First, different statistical methods were used in different studies. For example, in AusDiab study[43], the cutoff was 6.1% by visual inspection, but cutoff was changed when change-point models were used. Without any adjustment, a threshold of 5.2% was calculated by using a change point model. After adjustment for age, sex and systolic blood pressure, the threshold for HbA1c was observed at 5.6% (95%CI: 3.9-6.2, P = 0.092) and after further adjustment for diabetes duration, the threshold rose to 6.0% (3.9-7.0, P = 0.064). Study on Pima Indians, Egyptians and in DETECT-2 study, cutoff of HbA1c were determined without any adjustment. Second, the threshold of HbA1c depends widely on the definition of retinopathy. Mild retinopathy is not specific for DM as it has been documented in non diabetic individuals too. Thresholds of HbA1c for mild, moderate and severe retinopathy can differ.For example, in Malay population thresholds of HbA1c were 6.6% and 7.0% respectively for mild and moderate retinopathy[44]. Also, the criteria for grading of retinopathy was different in different studies.

Third, the distributions of HbA1c may not be the same for different ethnicities. For example, Tsugawa *et al*[41] in cross-sectional study examined the relationships between a HbA1c level and the prevalence of retinopathy in black and white United States adults. Two thousand eight hundred and four white persons and 1008 black persons above 40 years of age were included in the study. After adjustment for age, sex, hypertension, body mass index (BMI), family history of DM, and use of antidiabetes medications or insulin, the lowest HbA1c category for which the prevalence of retinopathy was significantly higher than the reference category (< 5.5%) was 6.0% to 6.4% for white persons (risk difference, 4.8% 95%CI: 0.5%-9.1%) and 5.5% to 5.9% for black persons (risk difference, 5.3%CI: 1.0%-9.5%). It was noted that the prevalence of retinopathy was higher at a lower HbA1c level in black Americans when compared white Americans. However, Bower *et al*[50] did not find any ethnic differences in the relationship of HbA1c with retinopathy in non-Hispanic white,non-Hispanic black and Hispanic American participants aged ⩾ 40 years from the 2005-2008 NHANES. Finally, differences in threshold of HbA1c might be due to lack of standardization of HbA1c measurements, especially in older studies.

HBA1C AND MACROVASCULAR COMPLICATIONS

Chronic hyperglycemia is a risk factor for adverse cardiovascular outcomes and mortality. A meta-analysis of 26 prospective studies assessed the association between HbA1c and major cardiovascular outcomes including all-cause mortality, incident cardiovascular diseases (CVD), CVD mortality, incident stroke and peripheral arterial disease. Only studies that followed up patients for more than 5 years were included. It was found that for every 1% increase in HbA1c, there was a 15% increase in hazard of all-cause mortality, 25% increase in CVD mortality, 17% in CVD, 17% in fatal coronary heart diseases and 29% increase in peripheral vascular diseases[51]. A positive dose response relationship was also noticed between HbA1c and the outcome measures and HbA1c was independent risk factor for adverse cardiovascular outcomes. Similar findings were noted in another meta-analysis by Selvin *et al*[52].

PREDIABETES AND RISK OF COMPLICATIONS

The association of complications is not restricted to

glucose levels above the diabetic threshold. It is a continuum, which continues in IGT and IFG range. Indeed, complications have also been documented in normal population,although of diminished magnitude. Various studies have looked into the paradigm of prediabetes forecasting the risks of micro and macro-vascular complications of diabetes.

PREDIABETES AND RISK OF DIABETIC RETINOPATHY

The occurrence of microvascular complications associated with established DM is well known. However, such complications of dysglycemia have also been noted in patients who currently fall within the spectrum of prediabetes. The Diabetes Prevention Programme followed up individuals known to have prediabetes and analysed a subset of them for development of diabetic retinopathy. Eight percent of patients had evidence of retinopathy as defined as Early Treatment Diabetic Retinopathy Study (ETDRS) level 20[53]. One percent of the study population noted to have mild/moderate diabetic retinopathy as defined by ETDRS level 35-43. The Blue mountains eye study, a population-based survey of common eye diseases conducted in Australia, screened 3275 participants without DM for retinopathy lesions using six field fundus photographs. Microaneurysms were seen in 6.8% of nondiabetic population[54]. These studies defined retinopathy based on the presence of absence of microaneurysms, and it is to be noted that they are not specific for diabetic retinopathy and may occur in patients with systemic hypertension.In some studies, they have been shown to be related to atherosclerosis and carotid disease.

A population-based cross sectional survey of prevalence of DM, risk factors and associated conditions was done in the AusDiab study[55]. All participants detected to have DM and prediabetes and few with normal glucose tolerance (as defined by WHO 1999 criteria) were screened for retinopathy. Fundus photographs included two fields per eye, namely the macula and nasal to disc were graded according to Wisconsin criteria. The prevalence of diabetic retinopathy was 6.7% (95%CI: 5.3%-8.4%) in patients with prediabetes[56]. The prevalence of retinopathy was 5.8% in the population with normal glucose tolerance (95%CI: 3.7%-8.5%)[57].

The gutenberg health study, is a prospective population-based observational study conducted in a single centre in Germany that initially included 15010 individuals with the aim of studying ocular, cardiovascular, psychosomatic and immune disorders. A sub-cohort of 5000 individuals were analyzed to study the prevalence of retinopathy in those diagnosed to have prediabetes as defined by HbA1c value ranging from 5.7%-6.4% and its association with cardiovascular risk factors. Twenty two percent of participants were diagnosed to have prediabetes based on the HbA1c criteria. Eighty three percent of those with prediabetes were assessed for evidence of retinopathy by 3-field fundus photograph, and 8.2% were found to have diabetic retinopathy. None of the participants had evidence of proliferative diabetic retinopathy. Though there was no statistically significant difference in the prevalence of cardiovascular risk factors between those with and without retinopathy, the number of participants with retinopathy was too small to draw any conclusion[58].

DIABETIC REINOPATHY CHANGES IN NORMOGLYCEMIA

However, the retinal vascular changes seen in diabetic patients, termed isolated retinopathy signs, are often seen in individuals without DM or hypertension. The prevalence of these signs has been documented to range between 2.6%-8.6% in individuals without DM or hypertension. Such isolated retinopathy signs are often transient and on follow-up of these individuals, 40%-70% of such signs may resolve spontaneously[59,60].

The Beaver Dam Eye study was a cross-sectional population-based study that investigated the association between retinopathy lesions and hypertension among non-diabetic individuals. Among the 4926 persons examined, 7.8% had evidence of retinopathy, and there was a significant association with systemic hypertension[61]. Similar prevalence was also seen in the Blue Mountains eye study where 3654 individuals from Sydney, Australia were screened for retinopathy using six field fundus photography. Retinal hemorrhages and microaneurysms were noted in 9.9% of individuals, and a significant positive relationship was noted between retinopathy and hypertension. However, DM was defined based on the FPG level > 7.8 mmol/L alone which could have resulted in mislabeling a significant proportion of individuals with DM as non-diabetics according to the current definitions[54].

A follow-up of this cohort, where 2335 persons were re-examined reported a cumulative 5 year incidence of retinopathy as 9.7% and no significant association was found between incident retinopathy and blood glucose level or hypertension. The lack of a demonstrable association with hypertension could have resulted from inadequate power of the study. Among those with retinopathy at baseline, 3.5% had developed DM during the intervening five year period, and the retinopathy lesions had regressed or remained unchanged in 72.3%[59]. The ARIC study had reported the three-year incidence of retinopathy in non-diabetic subjects as 2.9% and also showed an association between retinopathy and hypertension and fasting blood glucose levels. Forty-three percent of any retinopathy signs seen among patients at baseline had regressed at the end of three years. This was found to be related to lower levels of cardiovascular risk factors[60].

Whether these changes of retinopathy signify an increased risk of progression to DM is debatable. Most studies have shown no such association. However, retinopathy was predictive of incident DM in persons with a positive family history of DM during the follow-

up of the ARIC cohort. The incidence of DM was 10.4% among those with a family history of DM compared to 4.8% among those without a positive family history after a follow up of 3 years[62]. Similarly, the Beaver Dam study assessed the 15-year cumulative incidence of DM and hypertension among those with evidence of any retinopathy at baseline and found a significant association between incident DM and retinopathy among those < 65 years of age (24.3% *vs* 11.1%)[63].

PREDIABETES AND RISK OF NEPHROPATHY

The prevalence of nephropathy is increased in individuals diagnosed to have prediabetes compared to normal individuals. The NHANES data analysis revealed the prevalence of chronic kidney disease (CKD) (as defined by glomerular filtration rate (GFR) using "modification of diet in renal diseases" equation) in newly detected prediabetes to be 17.1% compared to 11.8% in those without DM and 24.2% in newly detected DM, after adjustment for age, gender and race. However, the diagnosis of prediabetes was based on measurement of FPG alone which could have underestimated the prevalence of prediabetes in the study. The other important risk factor for CKD, namely hypertension was documented based on self-reporting by study participants which could have again biased the results of the study. Nevertheless, the prevalence of CKD increased across the spectrum of dysglycemia[64].

Few studies have shown that early kidney injury characterized by hyperfiltration is seen in those with prediabetes. Among the 1560 individuals included in the Renal Iohexol Clearance Survey in Tromso 6 (RENIS-T6) study, it was seen that individuals with IFG had evidence of hyperfiltration (defined as GFR > 90th percentile determined by Iohexol method and adjusted for age, weight, height and use of renin-angiotensin inhibitors) when compared to those with normal glucose[65]. Similar results were obtained in the Huaian Diabetes Prevention program from China, where 5431 subjects were included to analyze the association between HbA1c level and renal hyperfiltration. The study had reported a positive correlation between HbA1c level and hyperfiltration independent of other parameters like age, sex, hypertension, BMI and lipid profile. The odds of hyperfiltration was 2.34 times higher in persons with HbA1c level of 6.21%-6.49% compared to those with A1c < 5.7%[66]. This indicates that chronic hyperglycemia is associated with hyperfiltration in addition to the acute effect of hyperglycemia that has been even in healthy subjects[67].

Microalbuminuria, another marker of kidney injury, has also been found to be associated with prediabetic state. A study from New Zealand determined the prevalence of microalbuminuria and its association with other risk factors like ethnicity, glycemic status, hypertension, obesity and life style factors. Individuals with IGT had a higher prevalence of microalbuminuria when compared to those with normal glycemic status (16.1% *vs* 4.0%) and glycemic status was found to be the most important determining factor of microalbuminuria in multivariate regression analysis[68]. However, contrary to the results of the above-mentioned studies, a study from Korea did not find any significant association between microalbuminuria and prediabetes. Forty-five percent of participants were diagnosed to have prediabetes based on ADA criteria for FPG and HbA1c in the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V). Though the prevalence of microalbuminuria was higher in the prediabetic group when compared to the normal group (6.3% *vs* 3.6%), this difference was not seen following the adjustment for hypertension[69].

PREDIABETES AND RISK OF NEUROPATHY

Nerve conduction study conducted in 58 subjects from India with prediabetes as defined by the WHO criteria detected evidence of neuropathy in 32.8% of subjects which was evaluated by quantitative sensory testing (QST) and autonomic function tests. Autonomic neuropathy was evident in 8% of individuals, and QST was abnormal in 27.6% of subjects[70].

PREDIABETES AND RISK OF CARDIOVASCULAR DISEASES

Both IGT and IFG are associated with an increased risk of developing adverse cardiac events. A few studies have shown that patients with IGT have a greater risk when compared to patients with IFG. The risk also seems comparable to those with DM. Individuals with prediabetes were shown to have evidence of subclinical arteriosclerosis as measured by cardio-ankle vascular index (CAVI) in a recent study from Japan. CAVI is a sensitive indicator of arterial wall stiffness that is independent of blood pressure changes[71]. The odds of having high CAVI score among those with prediabetes was 1.29 (95%CI: 1.11-1.48) in men and 1.14 (95%CI: 1.01-1.28) for women compared to 2.41 (95%CI: 1.97-2.95) in men and 2.52 (95%CI: 1.94-3.28) for women with DM[72].

Subclinical myocardial infarctions, defined as those unrecognized by the patient and the physicians are harbingers of major cardiovascular events in the future. The multi-ethnic study of atherosclerosis was instituted to study the prevalence and progression of subclinical cardiovascular disease in a population-based cohort from the United States[73]. In this cohort, the prevalence of unrecognized myocardial infarction detected based on electrocardiographic changes was found to be higher among those with IFG when compared to those with normal fasting glucose level (3.5% *vs* 1.4%) and this relationship persisted even after adjusting for other confounding risk factors[74].

Increased risk of cardiovascular disease and all-cause mortality with abnormal glucose metabolism was documented in the AusDiab study after a median follow-up of 5.2 years. IFG was found to be an independent predictor of CVD mortality with a hazard ratio of 2.5 (95%CI: 1.2-5.1) after adjusting for other risk factors for CVD. However, IGT was not found to be associated with increased CVD mortality[75].

A meta-analysis of studies evaluating the risk of coronary artery disease (CAD) associated with IFG as defined by the ADA and the WHO included 17 prospective studies. The risk of CAD was found to be increased in participants with IFG as defined by both criteria. The relative risk of CAD with IFG was 1.11 (95%CI: 1.02-1.21) using the ADA criteria and was 1.18 (95%CI: 1.10-1.28) when applying the WHO criteria. However, sub group analysis showed that the increased risk of CAD with IFG was not seen in studies that had excluded individuals with elevated 2-h plasma glucose. And further, the risk of CAD with IFG was not found to be significant when adjusted for other CAD risk factors[76]. A similar meta-analysis of studies analyzing the risk of stroke with prediabetes, an increased risk was seen in those studies which had defined prediabetes according to the WHO criteria (FPG 6.11-6.94 mmol/L). The risk was found to be increased in those with IGT and those with both IGT and IFG[77].

CONCLUSION

Current diagnostic criteria for DM or intermediate hyperglycemia is based on threshold of FPG, 2-h PG and HbA1c for diabetic complications,especially retinopathy. Controversies in diagnostic criteria are due to differences in inclusion criteria, different ethnic populations being studied, background prevalence of DM, definition of retinopathy used and statistical methods utilized. Therefore, there is a need to adopt uniform methodologies in studies across the globe to get universally comparable and interpretable results. Possibly, large longitudinal prospective studies involving subjects from different ethnicities, without diabetes and retinopathy at baseline will ideally help to identify the threshold of glycemic measurements (FPG, 2 h-PG and HbA1c) for future development of diabetes and its complications. Definition of retinopathy especially related to diabetes must be standardized universally. Further research is needed to understand better the pathophysiology of IFG and IGT. It is not well understood whether IFG and IGT are distinct metabolic abnormalities or they are parts of continuum. The factors predicting the development of future diabetes and its complications from IGT and IFG is also not well understood. This risk might be better assessed by the use of prediction scores which are weighted according to the glycemic measurements, other risk factors, and clinical features including complications. Finally, the extent to which,future DM and its complications, especially cardiovascular diseases can be prevented by adoption of modification of thresholds are not yet known.

New data from properly designed studies may help in revision of diagnostic criteria in future.

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MINIREVIEWS

In vivo corneal confocal microscopy in diabetes: Where we are and where we can get

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Abstract

In vivo corneal confocal microscopy (IVCCM) is a novel, reproducible, easy and noninvasive technique that allows the study of the different layers of the cornea at a cellular level. As cornea is the most innervated organ of human body, several studies investigated the use of corneal confocal microscopy to detect diabetic neuropathies, which are invalidating and deadly complications of diabetes mellitus. Corneal nerve innervation has been shown impaired in subjects with diabetes and a close association between damages of peripheral nerves due to the diabetes and alterations in corneal sub-basal nerve plexus detected by IVCCM has been widely demonstrated. Interestingly, these alterations seem to precede the clinical onset of diabetic neuropathies, paving the path for prevention studies. However, some concerns still prevent the full implementation of this technique in clinical practice. In this review we summarize the most recent and relevant evidences about the use of IVCCM for the diagnosis of peripheral sensorimotor polyneuropathy and of autonomic neuropathy in diabetes. New perspectives and current limitations are also discussed.

Key words: Corneal confocal microscopy; Neuropathy; diabetes; Cornea; New technologies

Core tip: Diabetic neuropathies are common, invalidating and often undiagnosed complications affecting a huge number of subjects with diabetes. *In vivo* corneal confocal microscopy is a novel, reproducible, easy and noninvasive technique that has been widely studied as a useful tool for the diagnosis of neuropathy. Promising data suggest its implementation in clinical and research practice will help to face the current health emergency related to nerve damages in diabetes.

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INTRODUCTION

Diabetic neuropathies are common and invalidating, but often undiagnosed, complications affecting up to 50% of subjects with diabetes[1,2]. Diabetic neuropathies encompass a wide spectrum of clinical and pathophysiological frameworks characterized by a progressive loss of nerve fibers, which may affect both somatic and autonomic nerves. While the rates of myocardial infarction, stroke, low-extremity amputations and end-stage renal disease due to diabetes are declining[3], this is not the case for trends in the incidence of neuropathies. An early diagnosis and correct staging of neuropathy is essential for risk stratification, therapeutic decisions and research purposes. To date screening and diagnosis of diabetic neuropathies mainly relies on symptoms questionnaires, clinical examination, quantitative sensory tests and reflex tests[4,5]. Nerve conduction studies should also be used to confirm the diagnosis and to assess the severity of the disease[2]. *In vivo* corneal confocal microscopy (IVCCM) is a non-invasive technique to visualize and analyze corneal anatomy at high magnification allowing the study of the different layers and cells of cornea, the most innervated organ of human body[6]. Several studies in the last decade investigated the use of IVCCM for the diagnosis of sensorimotor and, more recently, autonomic neuropathies[7]. In this review we aim to summarize the most recent and relevant evidences about IVCCM use in people with diabetes, focusing on strength and limitations future studies should overcome.

CORNEAL INNERVATION

The eye has historically been considered as a pivotal organ for the study of diabetes-related complications. The transparency of the ocular structures has always been used as a diagnostic tool to investigate and actually see *in vivo* vascular changes in the retina. More recently, increasing attention has been paid to corneal nerve anatomy for the study of human neuropathies. The cornea is provided of the densest innervation within the body receiving nerve fibers from 50-450 sensory trigeminal neurons *via* the ophthalmic branch of trigeminal nerve[8,9]. These fibers travel above the choroid, reach the limbus where they organize into a nerve plexus[10]. Corneal stromal nerves derive from the limbal plexus and branch into fibers with smaller diameter that establish close connections with keratocytes and corneal epithelial cells[11]. The fibers become denser and smaller in diameter as they reach the corneal apex creating a sub-epithelial dense network in the epithelium, known as sub-basal corneal nerve plexus.

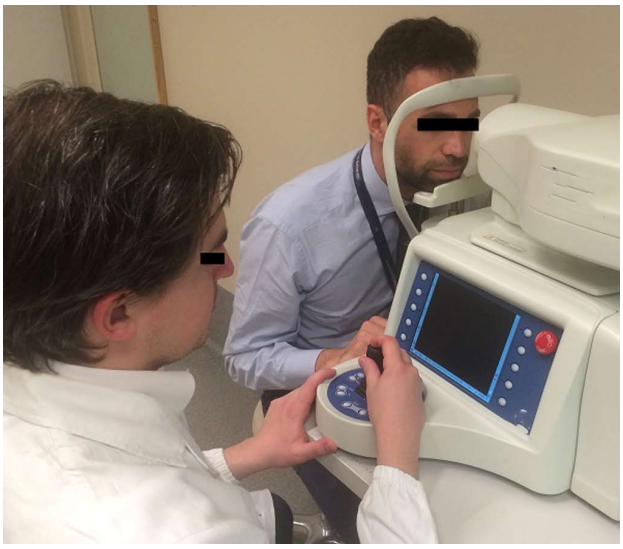

Figure 1 Acquisition of the images with *in vivo* corneal confocal microscopy. Patient is comfortably seated in front of the machine whilst the operator advances the scanning probe against the cornea with a joystick.

IVCCM

The introduction of IVCCM in ophthalmology (Figure 1) has represented a breakthrough for the study of ocular as well as systemic diseases since this diagnostic tool allows for a non-invasive and *in vivo* visualization of all the corneal layers, including nerves. There are currently three models of confocal microscope available, namely the slit-scanning, the tandem scanning and the laser scanning confocal microscope. They provide images with different resolution, contrast and magnification with high inter-device variability. However all of them result in high-resolution scans of the cornea. These features make IVCCM an ideal tool to investigate changes in corneal and ocular surface. It is used as an aid in the diagnosis and to monitor efficacy of therapies in different ocular diseases like, dry eyes, *Acanthamoeba* keratitis or keratoconus or following corneal surgery[12]. Several studies have also investigated the role of IVCCM as a diagnostic tool to be implemented for the assessment of several systemic diseases. Indeed, changes in the corneal sub-basal nerves have been shown to correlate with several neurodegenerative diseases, small fiber neuropathies, Fabry disease and other conditions causing peripheral neuropathy like diabetes, HIV-infection, genetic diseases, toxic drugs or autoimmune diseases[13].

IVCCM AND DIABETIC PERIPHERAL SENSORIMOTOR NEUROPATHY

Changes in corneal morphology including reduced thickness, thinner epithelium, irregular endothelium and reduction in corneal nerve bundles have been described in diabetes[14]. Therefore, qualitative and quantitative analysis of the sub-basal corneal nerve plexus by IVCCM

has been hypothesized to be a good method for the evaluation and quantification of nerve damages in people affected by diabetes. Several studies have been conducted to test this hypothesis in both type 1 and type 2 diabetes[7,15]. Overall, corneal nerve innervation has been shown impaired in subjects with diabetes, independently by the presence of overt neuropathy[16]. Interestingly, IVCCM was able in identifying early neuropathy also in subjects with pre-diabetes. Asghar *et al*[17] assessed corneal innervation in thirty-seven subjects with impaired glucose tolerance showing that IVCCM, but not electrophysiology studies, detected signs of nerve damages which correlated with neuropathy symptoms, neurological deficits and intraepidermal nerve fiber density (IENFD).

A close association between damages of peripheral nerves due to the diabetes and alterations in corneal sub-basal nerve plexus detected with IVCCM has been widely demonstrated by a number of studies. A landmark small cross-sectional study by Malik *et al*[18] showed corneal nerve fiber density, length and branch density were reduced in eighteen diabetic subjects with different grade neuropathy *vs* healthy controls, with a gradual reduction of these parameters with increasing neuropathy severity. Similarly, corneal nerve tortuosity was found increased in diabetics and in those with more severe neuropathy[19]. Subsequently several studies by this and other groups confirmed the efficacy of IVCCM for the identification of diabetic neuropathy in larger populations of type 1[20-23], type 2 diabetes[24] or both[25-27]. In particular, baseline features of the population enrolled in the LANDMark study, the largest study testing IVCCM in 242 type 1 diabetes *vs* 154 controls, confirmed the reduced corneal never fiber length in those with neuropathy[22]. Longitudinal results of this study are not yet available.

As cornea is innervated by small Aδ and C fibers, IVCCM was tested with good results as a surrogate marker of small fiber neuropathy[28]. Before IVCCM, the evaluation of IENFD by skin biopsy was the gold standard method to quantitatively assess small fiber damages, with obvious limitations for a routine implementation in clinical practice due to its invasiveness. A comparable diagnostic efficiency between IVCCM and IENFD in type 1 diabetes has been recently shown in a study by Chen *et al*[29] where the area under the receiver operator curve for the identification of neuropathy did not significantly differ between the two techniques.

Among all the parameters of corneal innervation evaluated by IVCCM, the great majority of published studies agree about the validity and the overall good reproducibility of corneal nerve fiber density and length. In particular, the latter was shown to be the best predictor of diabetic sensorimotor polyneuropathy in 81 subjects affected by type 1 diabetes, with an optimized threshold for sensitivity and specificity at 14.0 mm/mm^2[30]. This threshold, however, has to be applied taking into account the natural age-dependent variation in corneal nerve fiber length. On the contrary, corneal nerve beadings and tortuosity showed the highest inter and intra-individual variability, questioning the validity of these two measurements for the diagnosis of diabetic peripheral neuropathy[21]. However, the measurement of nerve tortuosity could be relevant to ameliorate the predictive value of fiber length, as tortuosity-standardized corneal nerve fiber length was better than non-standardized length in differentiating between individuals with and without neuropathy[31].

IVCCM AND DIABETIC AUTONOMIC NEUROPATHY

Diabetic autonomic neuropathy is a form of diabetic neuropathy that results from the damage of small (Aδ, B and C) nerve fibers. It represents one of the most overlooked but life-threatening complications of diabetes, associated with gastrointestinal, genitourinary, vasomotor and cardiac symptoms. In particular cardiac autonomic neuropathy affects up to 40% of diabetic patients and is associated with silent myocardial ischemia, stroke and increased mortality[5]. Because of the structural similarity between the corneal nerve fibers analyzed with IVCCM and the small fibers conducting autonomic signals, IVCCM has been recently tested as a diagnostic tool for autonomic neuropathies. We showed that subjects affected by type 1 diabetes with cardiac autonomic neuropathy, as evaluated by cardiovascular autonomic reflex tests (CARTs), had reduced corneal nerve fiber density and length when compared to peers without cardiac autonomic neuropathy and to healthy controls, independently of the presence of peripheral neuropathy[32] (Figure 2). Subsequently, Tavakoli *et al*[33] confirmed our observation in a population of both type 1 and type 2 diabetic subjects. Subjects were evaluated by the Composite Autonomic Symptom Scale (COMPASS), by CARTs, by sympathetic skin response, and by IVCCM. The Composite Autonomic Severity Score (CASS) was also calculated. Corneal nerve fiber density, length and branch density were significantly reduced in subjects with autonomic deficits than in those without. IVCCM showed moderate-to-strong correlations with COMPASS and CASS, with a good sensitivity and specificity for fiber length and fiber density for the diagnosis of diabetic autonomic neuropathy[33]. Similarly, corneal nerve innervation was found to be related to sudomotor function in subjects affected by type 2 diabetes[34]. Moreover, a significant correlation between corneal sensitivity and measures of cardiac autonomic function in subjects with type 1 diabetes was recently reported[35]. However, in the same study no significant relationship with sub-basal nerve density was found.

IVCCM IN DIABETES: WHERE WE CAN GET

A growing literature supports IVCCM as an innovative

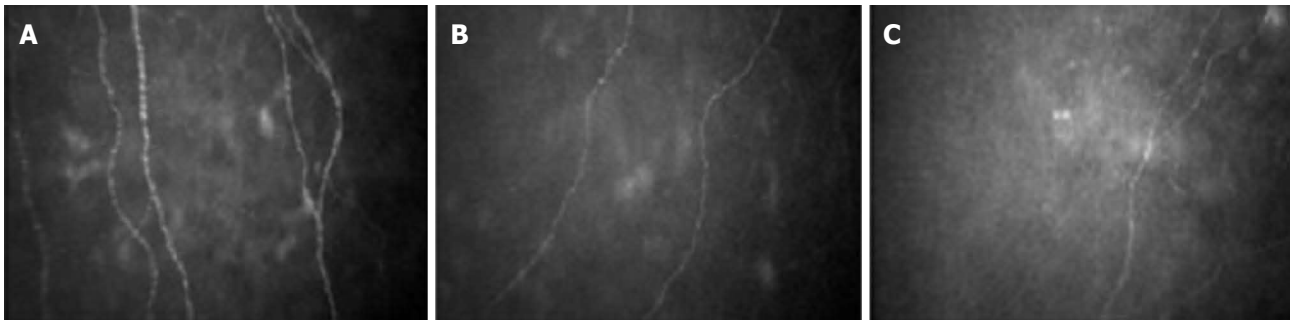

Figure 2 Corneal innervation evaluated by *in vivo* corneal confocal microscopy in a health subjects (A), in a subject affected by type 1 diabetes without cardiac autonomic neuropathy (B) and in a subject affected by type 1 diabetes with cardiac autonomic neuropathy (C). Nerve fiber density and length is reduced in people with type 1 diabetes and in those with cardiac autonomic neuropathy.

technique helpful to face diabetic neuropathies, which are prevalent complications of diabetes and cause of high healthcare expenditures, reduced quality of life, high morbidity and mortality. In particular IVCCM could have possible implications for the prevention of diabetic neuropathies and for research studies about its pathophysiology and treatments.

Prevention

Changes in the corneal sub-basal nerve plexus anticipate other clinical and electrophysiology signs of neuropathy[35,36]. Two longitudinal studies showed that lower corneal nerve fiber length predicts the onset of diabetic sensorimotor polyneuropathy in type 1 diabetic subjects followed-up for 3.5 and 4 years[37,38]. For the identification of new cases of neuropathy, the sensitivity and specificity of corneal nerve fiber length were 82% and 69%, respectively, with an optimal threshold of 14.9 mm/mm^2 in one study[37], and 63% and 74% with an optimal threshold of 14.1 mm/mm^2 in the other one[38]. This suggests IVCCM allows the identification of at-risk patients to implement preventive strategies such as tight glycemic control and multifactorial interventions. Indeed, a prospective cohort study in subjects with type 1 diabetes without overt neuropathy showed that modifications in the corneal sub-basal nerve plexus over 4 years of follow-up were related to clinical and metabolic factors such as age, HbA1c and HDL cholesterol. This highlights the capability of IVCCM for monitoring the efficacy of preventive strategies aimed to modify the natural history of diabetic neuropathy before symptoms and signs become measurable by classical screening tests[39].

Moreover, Petropoulos *et al*[40] showed that degeneration of corneal nerve fibers are detectable before other microvascular complications appear, questioning whether early detection of small fibers distress by IVCCM could also work as a precocious surrogate marker for vascular risk stratification as well as microalbuminuria or retinopathy. However, to date no studies have specifically investigated the predictive value of IVCCM with regards to the development of diabetic complications other than neuropathy.

Research tool

Besides the clinical implications, IVCCM could be a useful research tool to investigate neuropathy pathophysiology. The promising data showing early degeneration of corneal nerve fibers in impaired glucose tolerance and new onset type 2 diabetes[17,24,41] support the hypothesis the pathophysiology of diabetic neuropathy starts very early in diabetes[42]. Overall the data discussed so far pose IVCCM as a research tool to investigate the first steps of neuropathy, where other methods such as nerve conduction studies are not enough sensitive to detect pathological changes. Moreover, even though corneal nerve fibers have sensitive but not autonomic function, the above reported results about the association of IVCCM and diabetic autonomic neuropathy overall suggest that molecular cascades eventually leading to the damage of the sub-basal corneal plexus could also occur to nerves with similar structure such as the autonomic ones, even if they have different function. They also suggest that IVCCM is a surrogate easy and non-invasive marker of autonomic dysfunction, which mostly remains undiagnosed because of scarce implementation of the recommended diagnostic tests. However, these promising findings have still to be tested for their usefulness for cardiovascular risk-stratification in larger and homogenous populations.

Interestingly, some reports show that IVCCM is also able in detecting regeneration of small nerve fiber after therapeutics. IVCCM showed significant improvements in nerve morphology after pancreas transplantation[43], after simultaneous kidney-pancreas transplantation[44], after improvements in risk factors for diabetic neuropathy[45], in subjects treated with continuous subcutaneous insulin infusion[46] and in phase 2 studies[47]. These studies suggest IVCCM is novel noninvasive tool to establish early nerve repair consequent to medical intervention that is missed by current assessment techniques.

Current pitfalls and limitations

Some pitfalls still exist about the use of IVCCM for the diagnosis of diabetic neuropathies. In particular, an age-related decline in corneal nerve fibers density

and length occurs, claiming for age-standardized normative values. Moreover, there are uncertainties about racial differences in corneal nerve measures. IVCCM implementation and utility is also limited by the time and the expertise required for image analysis. Some arguments against IVCCM also claim a scarce reproducibility of corneal nerve measurements. In this regard, it has been recently shown preservation in the inter- and intra-observer reproducibility of fiber length measurements when using a fully automated analysis program, which also eliminates the need for trained analyst personnel and reduces the analysis time[25,48].

CONCLUSION

In conclusion, IVCCM currently represents a fascinating link between laboratory and clinical sciences through which diabetic neuropathies can be analyzed by assessing nerve density, tortuosity and length. We acknowledge our conclusions may be limited by the fact this manuscript is not a systematic review. However, to limit a possible selection bias, we carefully search throughout the literature for human studies testing IVCCM in people with diabetes and reported both positive and negative results, strength and limitations. As a result of our search, we reported that several evidences support the role of IVCCM as an easy and non-invasive clinical and research tool for the study of diabetic neuropathies, but some limitations including bias in image selection, reproducibility and the required expertise to perform the scan and read the images still need to be fully addressed.

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MINIREVIEWS

Diabetes mellitus and cognitive impairments

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Abstract

There is strong evidence that diabetes mellitus increases the risk of cognitive impairment and dementia. Insulin signaling dysregulation and small vessel disease in the base of diabetes may be important contributing factors in Alzheimer's disease and vascular dementia pathogenesis, respectively. Optimal glycemic control in type 1 diabetes and identification of diabetic risk factors and prophylactic approach in type 2 diabetes are very important in the prevention of cognitive complications. In addition, hypoglycemic attacks in children and elderly should be avoided. Anti-diabetic medications especially Insulin may have a role in the management of cognitive dysfunction and dementia but further investigation is needed to validate these findings.

Key words: Alzheimer's disease; Cognitive disorders; Dementia; Diabetes; Insulin

Core tip: Diabetes mellitus increases the risk of cognitive impairment and dementia. Impairment of insulin signaling is a critically important factor and may be the cornerstone of the development of these cognitive sequences regardless of diabetic status. Therefore, anti-diabetic medications especially insulin therapy may have a significant role in the management of various cognitive and mental dysfunctions.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common diseases whose prevalence is on the rise. It

is believed that within the next 30 years, the number of diabetic patients will double in comparison to the year 2000[1]. On the other hand, diabetes is amongst the diseases with higher complications (perhaps even the highest) and these complications lower the quality of life in patients significantly[2-4]. Diabetes is a systemic disease as it affects various body systems to some extent. For instance, diabetes can disrupt proper function in cardiovascular, gastrointestinal, immune and nervous systems. The functional impairment of peripheral nervous system can lead to diabetic foot and in worst cases to amputation and hence physical disability. Involvement of retina [diabetic retinopathy (DR)] can lead to loss of vision and blindness.

Adverse effects of diabetes on cognitive system and memory disorders have been noticed by researchers for a long time[2-4]. Equally, dementia is one of the most disabling public health problems. It affects the quality of life of demented patients and their caregivers. It also imposes a huge economic burden on countries. Therefore, identification of risk factors of dementia and the control of those factors is with utmost importance.

This review discusses the association between diabetes and the risk of cognitive impairment with more clinical aspects. Therefore, possible underlying mechanisms of cognitive impairment in diabetic patients will be discussed, and the effect of various treatments on prophylaxis and improvement of mental dysfunction will be reviewed.

OVERVIEW OF MEMORY AND COGNITION

Cognition is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses"[5].

Memory is the retention, recording, and process of retrieving knowledge. All knowledge gained from experience such as known facts, remembered events, gained and applied skills would be considered as memory[6]. Memory can be categorized into declarative and non-declarative memory. Declarative memory mostly corresponds to the learning and recalling new facts, events, and materials. Non-declarative memory refers to the many forms of memories that are reflective or incidental[6].

The "brain working memory" is defined as the ability to keep record of many bits of information at the same time and the recall of this information immediately if needed for subsequent thoughts[7]. When working memory is damaged, a wide range of cognition impairments occur and the patient will not be able to appropriately use his/her own information for thinking in different situations[6].

The majority of advanced cortical functions arise from association cortex. The main association areas are: (1) the parieto-occipitotemporal association area; (2) the prefrontal association area; and (3) the limbic association area[7].

Our knowledge about the mechanisms of thinking and remembering is little. It seems that each thought arises from simultaneous activation of many parts of the different areas in the brain such as cerebral cortex, limbic system, thalamus and reticular formation of the brainstem. The memory is the result of some events in the synaptic transmission by changing its basic sensitivity[7].

Constant neural activity that arises from traveling nerve signals to a temporary memory trace can create a "short term memory". A temporary chemical or physical synaptic change that lasts for a few minutes up to several weeks makes an "intermediate long term memory". Structural alterations in synapses occur when a "long term memory" is created and can be used weeks to years later[7]. The hippocampus and, to a lesser degree, the thalamus are responsible for deciding which thoughts are important enough to be saved as memories[7].

It is possible to acquire information about the patient's cognitive, behavioral, linguistic, and executive functioning, and memory through Neuropsychological tests. These data can be used in the diagnosis of cognitive disorders and for localization of the abnormality in the brain, as well as, the assessment of therapeutic effects of any treatment modality on the cognitive dysfunction. Neurocognitive domains and some examples for their assessment are categorized in the Table 1[8,9].

Neuropsychological evaluation measures the cognitive abilities in the patient quantitatively, and its results must be interpreted in the setting of the patient's: Age, education, gender, and cultural background. In addition, reliability, validity, sensitivity, and specificity of these tests are important aspects that should be considered.

ETIOLOGY OF COGNITIVE DISORDERS

Dementia and cognitive dysfunction have many causes. Alzheimer's disease (AD) and other degenerative diseases, vascular dementia, alcohol consumption, and certain drug abuse are some of these etiologies. Additional disorders that can cause memory loss and other cognitive impairments are listed in the Table 2[9].

ASSOCIATION BETWEEN DIABETES AND COGNITIVE DECLINE

Cognitive dysfunction with its wide range, from mild cognitive impairment (MCI) through dementia, is one of the chronic complications of diabetes mellitus[10]. Both diabetes and cognitive impairment occur more commonly at older age. There is strong evidence that T2D increases the risk of dementia in the form of multi-infarct dementia, AD and mixed type dementia. There are some close associations between diabetes and vascular dementia of above 100%-160% compared to

Table 1 Neurocognitive domains and some examples for their assessment[8,9]

Cognitive domain	Examples of assessments
Complex attention (sustained attention, divided attention, selective attention, processing speed)	Sustained attention: Maintenance of attention over time Selective attention: Maintenance of attention despite competing stimuli and/or distractors Divided attention: Attending to two tasks within the same time period Processing speed can be quantified on any task by timing it
Executive function (planning, decision making, working memory, mental flexibility)	Planning: Ability to find the exit to a maze; interpret a sequential picture Decision making: Performance of tasks that assess process of deciding in the face of competing alternatives (*e.g.*, simulated gambling) Working memory: Ability to hold information for a brief period and to manipulate it (*e.g.*, adding up a list of numbers or repeating a series of numbers or words backward) Mental/cognitive flexibility: Ability to shift between two concepts, tasks, or response rules
Learning and memory [immediate memory, recent memory (including free recall, cued recall, and recognition memory), very-long-term memory (semantic, autobiographical), implicit learning]	Immediate memory span: Ability to repeat a list of words or digits. Note: Immediate memory sometimes subsumed under "working memory" (see "Executive Function") Recent memory: Assesses the process of encoding new information (*e.g.*, word lists, a short story, or diagrams) Free recall (the person is asked to recall as many words, diagrams, or elements of a story as possible Cued recall (examiner aids recall by providing semantic cues such as "list all the food items on the list" Recognition memory (examiner asks about specific items, *e.g.*, "Was 'apple' on the list?") Semantic memory (memory for facts) Autobiographical memory (memory for personal events or people) Implicit (procedural) learning (unconscious learning of skill)
Language [expressive language (including naming, word-finding, fluency, and grammar and syntax) and receptive language]	Expressive language: Confrontational naming (identification of objects or pictures) Fluency [*e.g.*, name as many items as possible in a semantic (*e.g.*, animals) or phonemic (*e.g.*, words starting with "f") category in 1 min] Grammar and syntax (*e.g.*, omission or incorrect use of articles, prepositions, auxiliary verbs) Receptive language: Comprehension, performance of actions/activities according to verbal command
Perceptual-motor (includes abilities subsumed under the terms visual perception, visuoconstructional, perceptual-motor, praxis, and gnosis)	Visual perception: Line bisection tasks can be used to detect basic visual defect or intentional neglect Visuoconstructional: Assembly of items requiring hand-eye coordination, such as drawing, copying, and block assembly Perceptual-motor: Integrating perception with purposeful movement (*e.g.*, rapidly inserting pegs into a slotted board) Praxis: Integrity of learned movements, such as ability to imitate gestures (wave goodbye) or pantomime use of objects to command ("show me how you would use a hammer") Gnosis: Perceptual integrity of awareness and recognition, such as recognition of faces and colors
Social cognition (recognition of emotions, theory of mind)	Recognition of emotions: Identification of emotion in images of faces representing a variety of both positive and negative emotions Theory of mind: Ability to consider another person's mental state (thoughts, desires, intentions)

AD which is about 45% to 90%[10]. The long-term risk of dementia increases in patients with diabetes by a factor of two[11]. T2D also increases the risk of progression of MCI to dementia[11]. Even in pre-diabetic state; there is an increased risk of AD and dementia which are not related to the future development of diabetes[10]. About 80% of people with AD may have diabetes or impaired fasting glucose[12]. There is a faster deterioration of cognition in diabetic patients rather than non-diabetic elderly ones[13]. Diabetes is associated with 1.5-2 fold increased risk of cerebrovascular accidents[14] and the relative risk of stroke increases 1.15 (95%CI: 1.08-1.23) for every 1% increase in HbA1C[15].

In recent years, the relation of diabetes to memory disorders has been well established. In 2011, Wessels *et al*[16] published results of their comprehensive prospective study on a large sample size from 1992 to 2007. Patients in this cohort were examined at baseline and five follow-up assessments throughout the 15 years of study. During each evaluation, participants were given the Community Screening Interview for Dementia as part of a home visit. They followed up 1702 subjects and showed that diabetes reduced their cognitive capabilities *via* cardiovascular disruption[16]. The results of the Edinburgh Type 2 Diabetes Study that was conducted for evaluation of this correlation were published in 2013. At baseline, any clinical and subclinical macrovascular diseases including cardiovascular event history, carotid intima-media thickness, ankle brachial index, and serum N-terminal probrain natriuretic peptide (NT-proBNP) were evaluated. Seven neuropsychological tests were also done at baseline, and after 4 years. They found that stroke and subclinical markers of cardiovascular and atherosclerosis are associated with cognitive decline in older patients with type 2 diabetes (T2D)[17].

Recent research collaboration between Mayo Clinic and Shanghai was reported in 2015. In this study, involving a considerable number of patients, the effect of diabetes on the cognitive function of patients was strongly evident. This was, of course, irrespective of patients' gender, age and possible cardiovascular risk factors[18].

In one study, the relationship between T2D and cognitive impairment had been evaluated and the subjects with diabetes had lower MMSE score than those without diabetes ($P < 0.01$)[19]. Diabetes was

Table 2 Memory loss and cognitive impairment etiology[9]

Degenerative disorders including Alzheimer's disease
Vascular dementia
Depression and anxiety
Medication side effects
Disturbed sleep
Hormones
Metabolic disorders
Diabetes
Alcohol abuse
Lyme disease
Hippocampal sclerosis
Subdual and epidural hematomas
Vitamin B12 deficiency
Seizures
HIV associated neurocognitive disorder
Hashimoto's encephalopathy

HIV: Human immunodeficiency virus.

also associated with increased odds of cognitive decline as determined by MMSE scores [odds ratio (OR), 1.9; 95%CI: 1.01-3.6]. Also, a statistically significant correlation between the duration of the disease and cognitive dysfunction was observed (P = 0.001). The same correlation was also found for the quality of diabetes control (P = 0.002).

In a different study that was carried out on 4206 subjects by Qiu *et al*[20], they investigated whether and the extent to which vascular and degenerative lesions in the brain mediate the association of diabetes with poor cognitive performance. They assessed cortical and subcortical infarcts and higher white matter lesion volume. They also evaluated neurodegenerative processes on magnetic resonance images. The results of this cross-sectional study showed that diabetic patients' speed in processing and executive functions was markedly lower than others. However, their memory function score was not any better either[20].

The role of diabetes in neurodegeneration has been confirmed by neuroimaging and neuropathological studies. MRI studies have shown that T2D is strongly associated with brain atrophy[21]. The rate of global brain atrophy in T2D is up to 3 times faster than in normal aging[22,23].

SPECIFIC EFFECTS OF T1D AND T2D ON COGNITION

Diabetes Mellitus is related to 40% higher rate of MCI; both amnestic and non-amnestic[24]. This is especially true when diabetes starts before the age of 65, or when the disease is more than 10 years. Treatment with insulin and the presence of diabetes complications such as retinopathy are other risk factors[25,26].

In children, the relationship between T1D and cognitive disorders is also reported[27]. Cognitive flexibility, visual perception, psychomotor speed, and attention are the main domains which are mostly affected early (on within 2 years in T1D), among which the mental slowing is the principal deficiency. Learning and memory function seem to be intact even in a prolonged hyperglycemia in T1D[25]. Young age is an important risk factor in developing cognitive deficits in T1D. It seems that children whose disease is diagnosed under the age of 7 are at a greater risk for more severe cognitive dysfunction[28].

Single-photon emission tomography in diabetic patients shows an abnormality in many brain regions, which correlate especially with diabetic microvascular complications and poor glycemic control in T1D. However, there is no strong evidence to support the importance of brain perfusion abnormalities in the development of cognitive dysfunction in T1D[29].

In both types of diabetes, neural slowing, cortical atrophy and microstructural abnormalities in white matter are prominent[24].

The effect of diabetes on patients' mood and temper has also been investigated. In a recent article by Ho *et al*[30], they have pointed out the effects of diabetes on hippocampus neurogenesis and depression and the resulting cognitive.

DR AND COGNITIVE IMPAIRMENT

It has been shown that there is an association between DR and cognitive impairment. According to some studies, the vascular complications of diabetes such as retinopathy are the most important predictors for the cognitive decline. Based on the similarity in anatomy, physiology, and embryology of cerebral and retinal small vessels, this association is particularly interesting[31].

In a systematic review which analyzed three studies, it has been proven a near three fold increased risk of cognitive impairment in patients with DR. However; the association between the severity of DR and cognitive decline was not clearly demonstrated. Only one study showed that the men with more severe cognitive impairment had greater degree of retinal involvement. The recent memory and the verbal learning were the most defective cognitive domains in these studies[32].

Some studies have reported an association between cognitive impairment and general (not diabetic) retinopathy independent of other cardiovascular risk factors but underlying etiology has not been clearly identified[33,34]. The higher prevalence of cognitive impairment even in those with non-DR provides some clues to investigate the underlying mechanism for this association in wider metabolic abnormalities (hypertension, dyslipidemia, and inflammatory stress) rather than a pure glucotoxic effect[32].

In a longitudinal study from using Action to Control Cardiovascular Risk in Diabetes (ACCORD) data, the association between DR and cognitive impairment in T2M was confirmed. This study showed that cognitive dysfunction was a predictable consequence of DR. In the ACCORD data, the patients with DR had lower Mini-Mental State Examination (MMSE) score[35].

In one cohort study by Crosby-Nwaobi *et al*[36], they

compared patients with Proliferative Diabetic Retinopathy with patients with Non Proliferative Diabetic Retinopathy or no retinopathy. They found that there is an inverse relationship between the severity of DR and the severity of cognitive impairments: Those with no or mild form of DR had more deficits in attention/orientation, language, memory, and visuospatial ability fields in comparison with patients with severe DR. However; their study showed that cognitive impairment was more prominent in those with mild retinopathy than those without retinopathy[36].

BRAIN IMAGING IN DIABETES

Brain imaging can be an important tool to clarify the underlying pathogenesis for cognitive impairments in diabetic patients. Some researchers have been reported both focal and global cerebral changes[37].

Slight brain structural abnormalities have been reported in T1D[25,38]. A study showed that the gray matter density of patients with T1D was less than the control group and this finding correlated with severe hypoglycemic attacks and higher HbA1c levels. This assessment was performed with voxel-based morphometry - a well-known quantitative MRI technique[25,38].

The direction of water diffusion in tissues is measured by using diffusion tensor imaging (DTI) that is an index for the integrity of white matter[25]. DT1 shows microstructural abnormalities particularly in the optic radiations and posterior corona radiata in T1D patients. These findings correlate with longstanding diabetes and high concentrations of HbA1c[39]. These abnormalities may be the underlying pathogenesis in the mental slowing that is the main cognitive problem in T1D[40]. DT1 Technique will be a good research tool for future studies in this setting.

There is a relationship between T2D and lacunar infarcts/cerebral Atrophy. This association between T2D and white matter lesions is less clear[37]. It was reported that hippocampal atrophy is a consistent neuroimaging finding in patients with T2D[41], but a relatively recent study that evaluated the data from one cohort study and two case control studies, concluded that these patients did not have any specific vulnerability to hippocampal atrophy. Nevertheless; they have greater global brain atrophy compared to controls[42].

DIABETES MELLITUS, AD AND INSULIN ROLE

T2D is a condition in that elevated blood glucose levels is resulted from increased glucose production by liver, reduced insulin production by pancreas and "insulin resistance" in which insulin responsiveness is decreased due to abnormal expression of the insulin receptors[43].

The idea that AD is a metabolic disease in which brain glucose utilization is impaired is supported by some evidences. Conversely; amyloid precursor protein (APP) and amyloid-β-peptide (Aβ) have been shown to induce mitochondrial activity defects and increase oxidative stresses that are able to impair key players of the glucose metabolic pathway[44,45].

The prevalence of AD may be higher in patients with diabetes; however, the ORs are lower than those for vascular dementia[46]. In recent years; there are a number of studies that show a connection (*via* comparing pathologic samples) between T2D and AD. Scientists consider a key role for oxidative stress in development of AD in patients with diabetes Mellitus[43]. Diabetes Mellitus contributes to AD development by favoring tau hyperphosphorylation, accumulation of Aβ, increased oxidative stress and oxidative damage and mitochondrial dysfunction[44]. In this regard, the analysis of oxidation and damage of protein belonging to metabolic pathways (glucose metabolism) might be of interest in understanding the potential molecular mechanisms targeted by oxidative stress that trigger common features between T2D and AD. Different studies have shown that insulin resistance and reduced activation of insulin receptors with decreased neuronal plasticity mechanisms and survival are the main abnormalities in AD brain[43,47-49]. Figure 1 illustrated some aspects of this mechanism[43].

T2D is a heterogeneous disorder that is accompanied with numerous comorbidities like hypertension and dyslipidemia, where each has the same adverse effects on the cognitive function[50]. In addition, other insulin resistance situations including obesity and metabolic syndrome are associated with a wide range of cognitive dysfunction and progression of AD[25,51].

Long term effects of insulin resistance consist of hypertension, malignancy and cardiovascular disease. It has been shown that insulin resistance has a negative correlation with verbal cognitive performance[25].

Thus, insulin resistance seems to be the fundamental feature that links T2DM to the future development of AD. The biochemical and molecular changes in AD is similar to the effects of NASH (nonalcoholic steatohepatitis) on the liver and T2D on the skeletal muscles[52]. Long term outcomes of insulin resistance include cellular energy defect, high plasma lipids and hypertension[52]. In Addition, chronic hyperinsulinemia predicts later development of T2M[53]. Insulin resistance is also a definite predictor of serious conditions such as cerebrovascular and cardiovascular diseases, hypertension, and malignancy[52]. Hyperinsulinemia is linked to some other diseases with different primary target organs include: Obesity, nonalcoholic fatty liver disease, metabolic syndrome, polycystic ovarian disease, age-related macular degeneration. Overlap among these diseases often occurs and its rate is increasing with obesity epidemics[52].

INSULIN SIGNALING

There is significant amount of evidence demonstrating that dysregulation of insulin is a key element in trig-

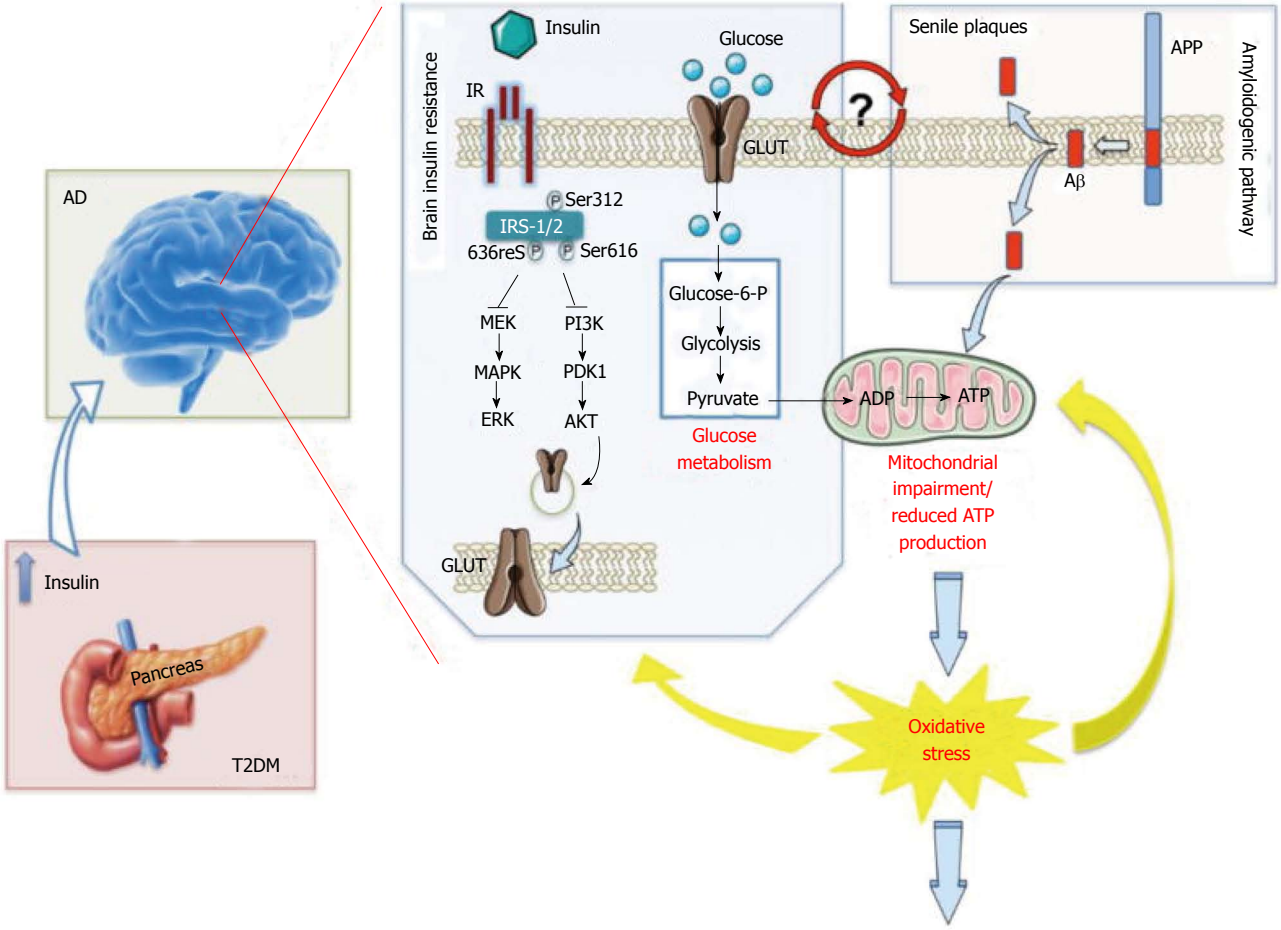

Figure 1 Increased oxidative stress level as a central event driving insulin resistance in Alzheimer' disease brain[43]. Persistently high levels of circulating insulin [as observed in the first phase of type 2 diabetes mellitus (T2DM)] may exert a negative influence on memory and other cognitive functions by down regulation of insulin receptors (IR) at the blood brain barrier and consequent reduced insulin transport into the brain [as observed in Alzheimer's disease (AD)], thus leading to insulin resistance. From a molecular point of view, the lack of interaction between insulin and IR is associated with an increase of the inhibitory phosphorylation on insulin receptor substrate-1/2 (IRS1/2) on Ser312, 616 and 636, which, in turn, negatively impacts on the two main arms of insulin-mediated signaling cascade: The PI3K and the MAPK pathways, both involved in the maintenance of synaptic plasticity and cell stress response. Furthermore, turning off insulin signaling results in impaired glucose transport (reduced translocation of the glucose transporter at the plasma membrane) and metabolism thus promoting an alteration of mitochondrial processes involved in energy production. In turn, impairment of mitochondria functions leads to a vicious circle in which reduced energy production is associated with an increase of reactive oxygen and nitrogen species (ROS and RNS) responsible for the oxidative/nitrosative damage of mitochondria as well as other cellular components. In addition, increased Aβ production and accumulation, which represents a key feature of AD pathology, also promotes mitochondrial impairment. Moreover, insulin resistance-associated impairments in glucose uptake and utilization are associated with increased endoplasmic reticulum (ER) stress, which deregulate lipid metabolism, causing accumulation of toxic lipids in the brain. All these events contribute to the increased oxidative stress levels responsible of neurodegeneration observed in AD brain. Although insulin resistance and Aβ production can be considered leading causes of the rise of oxidative stress, this latter, in turn, promotes IRS-1/2 Ser-312, -616 and -636 phosphorylation as well as the oxidative damage of protein involved in glycolysis, the Krebs cycle and ATP synthesis that are crucial events in the reduction of glucose metabolism and thus insulin resistance. Finally, because insulin resistance is associated with increased Aβ production and Aβ production is postulated to be responsible for the onset of insulin resistance, it remains to be clarified whether insulin resistance is a cause, consequence, or compensatory response to Aβ-induced neurodegeneration. ADP: Adenosine diphosphate; APP: β-Amyloid precursor protein; ATP: Adenosine triphosphate; AKT: Akt also known as protein kinase B (PKB); ERK: Extracellular signal-regulated kinase; GLUT: Glucose transporter; MAPK: Mitogen-activated protein kinase; MEK: MAPK/Erk kinase; PDK1: 3-phosphoinositide-dependent protein kinase 1; PI3K: Phosphoinositide 3 kinase.

gering of neurodegeneration in T2D. Insulin binds to a specific receptor at blood brain barrier and transport into the CNS. It is shown that an acute increase in serum insulin levels is associated with an increase in CSF and intracellular insulin levels[54,55]. Also, it is reported that chronic hyperinsulinemia is associated with downregulation of insulin receptor at blood brain barrier[54] which decrease brain insulin levels and consequently trigger or accelerate the process of neural aging and neurodegeneration[54,55]. Studies have shown that hyperinsulinemia causes an increase in Aβ levels as well as the inflammatory agents[56] and alter the metabolism of amyloid in the brain[46-57].

It seems, insulin has a neurotropic role in the brain. Insulin accomplishes this role by binding to insulin receptors on the cell surface. It is interesting that most of insulin receptors in the brain are on the surface of the cells, located in anatomical regions that are involved in memory formation. So it is postulated that insulin might play an important role in the memory system[54].

Insulin activates secondary messengers after binding to receptors. The most important of these secondary

messengers are phosphatidylinositol-3-kinase and Akt[54]. Activation of Akt causes inhibition of GSK-3β, which is an important kinase that phosphorylates tau. In fact, it is shown that under normal conditions, insulin inhibits tau phosphorylation and tau fibril production and low CSF insulin levels are associated with an increased neurofibrillary tangles[54,55]. Neurofibrillary tangles load is the best pathological marker of severity of dementia in AD.

Additionally, it's known that Aβ protein is degraded by several enzymes. The most important of these enzymes are neprilysin and insulin-degrading enzyme (IDE)[58]. Both insulin and Aβ protein can bind to IDE and it is shown that insulin has higher affinity to IDE[54]. It is shown that hyperinsulinemia might inhibits peripheral degradation of Aβ protein[59]. High level of Aβ protein can lead to an increase transport of this protein across blood brain barrier, which is shown to be associated with an increased production of senile plaques in the brain[59].

In conclusion, it is hypothesized that serum hyperinsulinemia is associated with lower level of insulin and higher level of Aβ protein in the brain, resulting in more neurofibrillary tangles, senile plaques, and possibly with impaired cognitive state.

IS AD A TYPE OF DIABETES MELLITUS?

AD is considered as type 3 diabetes by some investigators because the corner stone of pathogenesis of abnormalities in AD has strong similarity with T1D and T2D. Like T1D, insulin deficiency is a part of underlying mechanisms in AD and like T2D, AD is associated with insulin resistance in early stage of development[52,60,61]. Consequently, AD can be considered as the brain form of diabetes[52].

Nevertheless; Talbot *et al*[62], reported some evidence that considering AD as a type of diabetes is not completely true due to the following: First, hyperglycemia but not insulin resistance is the main key diagnostic feature of diabetes, and CSF glucose is not elevated in AD patients. Second, decreased glucose metabolism in the brain AD cases is not a direct consequence of brain insulin resistance. Instead of that, postsynaptic neurotransmission changes due to reduced insulin signaling are responsible for abnormal glucose metabolism in the AD brain. Third, brain insulin deficiency in the AD patients has not been established from the review of different studies, and only some of them have shown this decrement[62].

OTHER MECHANISM OF COGNITIVE IMPAIRMENT IN DIABETES MELLITUS

Vascular etiology

T2D is a risk factor for atherosclerosis and small vessel disease, so it clearly increases the risk of multi-infarct dementia and mixed type dementia. Other risk factors of vascular disease contribute to the development of dementia in patients with T2D, probably by vascular involvement. It has been shown that in patients with T2D, presence of hypertension, signs of microvascular diseases such as lacuna, DR and microalbuminuria or macrovascular complications such as cerebral infarcts increase the risks of dementia[54,63].

Chronic inflammation

Chronic inflammation is present in many patients with diabetes and insulin resistance is associated with increased levels of inflammatory cytokines, which elevated levels of inflammatory cytokines are associated with the worsening of the cognition in patients with diabetes[46,64].

Genetic

Brain changes and reductions in cognitive scores are most pronounced in patients with diabetes who have the Apo E epsilon 4 allele. The genetic factors contribute to dementia in T2D[65].

THERAPEUTIC APPROACHES

According to the long term prospective studies, good control of diabetes is beneficial in the reduction of cognitive decline in T1D[25,29], but the effect of this approach in T2D is controversial[66-70]. In one cohort study, there was a greater decline in cognitive impairment in patients on anti-diabetic medications and combination therapy was more effective than monotherapy[69].

One substudy of the ACCORD trial that followed up a large number of diabetic patients for 40 mo, showed no benefits from aggressive glucose control on the cognitive function[70]. In addition; three trials showed that intensive glycemic control has no benefit on the macrovascular events in T2D[66-68].

Association between cognitive decline and hypoglycemic attacks has been studied in some trials but the results are different. Overall, it seems that it is not a risk factor in T2D in carefully managed follow up studies. However, the prevention from hypoglycemia in the elderly is necessary, because it can cause more severe organic brain damage due to pre-existing atherosclerosis[71]. Also, it is true that, hypoglycemia may be a risk factor in children with diagnosed T1D within the first few years of life[25]. However, recurrent severe hypoglycemia is a significant preventable risk factor in these age groups and individualization of treatment, especially in the elderly, has a potential role in preventing hypoglycemia and consequently cognitive decline. While diabetes *per se* has a major impact on the elderly, the medications and the risk of hypoglycemia prevent optimization of glycemic treatment[72].

In one study, daily acute glucose fluctuation was an independent factor for cognitive dysfunction in T2D[73]. In another study, there was an association between cognitive impairment and postprandial hyperglycemia.

There was a greater decline in cognitive impairment after adjusting for postprandial hyperglycemia[74].

The thiazolidinedione classes of anti-diabetic medications are insulin sensitizers that work by making the cells more sensitive to insulin. Most of the research has focused on the effect of thiazolidinedione on improvement of cognitive function. The findings suggest that there is continuous beneficial effect of insulin sensitizers on cognition. Its effect is more pronounced on neuron action by reduction of apoptosis, protecting neurons from oxidative stress and reducing plaque formation and inflammation in mice brain models. Despite these findings, clinical trials in human are disappointing[10].

Insulin action has a contributing factor in cognitive function. Both insulin resistance and hyperinsulinemia are associated with cognitive impairment[71]. Excessive hyperinsulinemia exacerbates inflammation. Hyperinsulinemia enhances neurotic plaque formation[75]. Insulin secretion reduction is also associated with the onset of AD. Insulin definitively is connected with AD pathology and vascular dementia[76].

Intranasal insulin was effective in the improvement of memory function in memory impaired adults, in some studies[9]. Indeed, about 50% of all adults older than 60 years, even in the absence of diabetes, are insulin resistant[56]. It seems insulin puts its effect on cognitive function by modulation in aggregation of APP metabolites like beta amyloid peptide in neurotic plaques. On the other hand, factors associated with insulin resistance are suggested to be important in pathogenesis of AD. As it has been shown, Apo E negative patients are less sensitive to insulin which makes them in need for a higher level of insulin to facilitate an effective memory function in AD[77].

To date, there are few clinical data on the efficacy of metformin in AD and because of conflicting results regarding the effect of metformin in the improvement or deterioration of cognitive impairment, it needs to be clarified by a clinical placebo- controlled trial[78].

Other than hyperglycemia, midlife hypertension, midlife obesity, smoking, depression, and physical inactivity are attributable risk factors in AD and a 25% reduction in all of these factors could reduce the number of dementia by up to 3 million[79]. Large scale studies have shown that: Good control on blood pressure and lipid profile as well as glucose control will prevent vascular disease progression[80].

CONCLUSION

There is strong evidence that diabetes increases the risk of cognitive impairment and dementia. Insulin signaling dysregulation may be an important contributing factor in AD pathogenesis. In addition, diabetes is a risk factor for atherosclerosis and small vessel disease. It clearly increases the risk of vascular dementia. Good control of diabetes is beneficial in the reduction of cognitive decline in T1D, but the effect of this approach in improving cognitive outcomes in T2D is weak. Therefore; optimal glycemic control in T1D, identification of diabetic risk factors, and prophylactic approach in T2D are very important in the Prevention of cognitive complications. Lifestyle intervention such as proper diet and physical activity is the most important approaches in this way.

As the brain dysfunction in AD could be the result of disturbance in glucose metabolism and its dysregulation regardless of the diabetic status, future research with focus on anti-diabetic medications may open a new horizon for the prevention and management of AD. In addition, due to similarity in molecular and biochemical base of T2M and AD, more investigations in the domain of insulin resistance spectrum disorders provide an opportunity to find novel treatment strategies. These new approaches will be based on the improvement in the understanding of the pathogenesis of these fundamentally related disorders.

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