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REVIEW

Type 2 diabetes and quality of life

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Abstract

It is true that a primary goal of diabetes early diagnosis and treatment is quality of life (QoL). The term QoL is still confusing but it is agreed that it composes of four components: The physical component, mental, cogitative component, psychological and social component. Many articles have been written addressing those four components. During the last five years 15500 articles and reviews have been written addressing diabetes and coronary arterial disease, 16100 addressing diabetes and renal function, 28900 addressing diabetes and retinopathy, 16800 addressing diabetic foot ulcers and other 26300 addressing diabetic neuropathy. Moreover 17200 articles are dealing with diabetic sexual dysfunction, 24500 with the correlation of diabetes and depression 17500 about diabetes and dementia, only 1 about diabetes and family functioning and 1950000 about diabetes and QoL, indicating the worldwide interest. In order to confront this metabolic anomaly and its consequences, researchers developed numerous generic and disease specific psychometric tools. With the aid of those psychometric tools the scientific community has started to realize the gruesome effect of diabetes on patients' lives. Diabetic's QoL becomes worse when complications start to develop or comorbidities coexist. Dominant amongst complications, in health-related quality of life (HRQoL) lowering, but not related to risk factors (genetic, the weight of birth, or others) is coronary arterial disease followed by renal failure, blindness, and the combination of micro- and macro-vascular complications and in some studies by sexual dysfunction. Moreover many are the comorbidities which deteriorate further the effect of diabetes in a patient life. Among them obesity, hypertension, dyslipidemia, depression, arthritis are the most common. Most intriguing field for research is the interaction of diabetes and depression and in some cases the progression to dementia. Many aspects and combinations of actions are under researchers' microscope regarding the improvement of HRQoL scores. Until now, the studies performed, have demonstrated little to moderate benefit. More of them are needed to draw safe conclusions on the topic of the best combination of actions to optimize the HRQoL scores.

Key words: Type 2 diabetes; Quality of life; Diabetes co morbidities; Diabetes complications; Dementia; Diabetes type 3

Core tip: Although numerous articles and reviews are written about diabetes every year regarding epidemiology, complications, therapies, comparisons of treatments, health strategies, literature data on diabetic patient's quality of life and how much it is actually affected by complications, comorbidities or different treatments are limited. The current review is focused on: (1) the way patients perceive the changes in different aspects of quality of their lives as recorded by numerous psychometric tools and scales; (2) on the similarities and differences among studies performed worldwide along with the problems and caveats in research; and (3) on aspects intriguing but demanding further research as the effect of diabetes in family life or the common metabolic pathways between diabetes and dementia (recently called also diabetes type 3).

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INTRODUCTION

Diabetes is the increasingly growing metabolic threat of our contemporary era. Diabetes was first described[1] in an Egyptian manuscript from 1500 BC, mentioning "too great emptying of the urine"[2]. Later on, Indian physicians described also the disease and classified it as honey urine by the fact that ants were attacked by patient's urine[2]. The term "diabetes" or "to pass through" was first used in 250 BC by the Greek Apollonius of Memphis[2]. Diabetes type 1 and 2 were recognized for the first time as separate conditions by the Indian physicians Sushruta and Charaka in 400-500 BC, linking type 1 diabetes with youth and type 2 with obesity[2,3]. The term "mellitus" or "from honey" was added by Thomas Willis in the late 1600s because of the sweet taste that urines from diabetic patients had[2]. The first complete clinical description of diabetes was given by the Ancient Greek physician Aretaeus of Cappadocia (1st century AC), who also noted the excessive amount of urine a typical sign of diabetes.

The disease's description has accompanied the human race throughout the centuries. It is found in medieval Persia in Aviccena's *The Canon of Medicine*, in the Roman Empire with Galen describing two cases of diabetic patients during his career[2]. Diabetes was also introduced into Korean and Japanese medicine under the Chinese name táng niào bìng, meaning "sugar urine disease". Although diabetes has been recognized since antiquity, pathogenesis of the disease was understood about 1900[4] while insulin was discovered by Canadians Frederick Banting and Charles Bestthe in 1921 and was first used in 1922[2].

It is well established that the prevalence of diabetes has increased in the developed and developing countries during the last four decades. That is a result of the abundance of food, the consequent change of our dietary habits and the lack of exercise. According to International diabetes Federation, nowadays, one every 11 adults has diabetes (415 million worldwide). By 2040, one adult in 10 (642 million worldwide) will suffer from diabetes. One in 7 births is affected from gestational diabetes and 542000 children worldwide have type 1 diabetes[5]. Additionally every 15 s a person dies from diabetes and the 12% of the global expenditure is spent on diabetes. What is fearful is that 46.5% of adults with diabetes are undiagnosed! In a recent Greek study an age- and sex-adjusted prevalence of diabetes of 10.6% was found, while the prevalence of undiagnosed diabetes was 34%[6].

Progression of diabetes, and especially poor glycemic control, leads to numerous potentially life threatening complications. Almost half of the adults with chronic kidney disease are derived from diabetic population. Likewise, 9.8% of diabetics have experienced heart attack, 9.1% suffer from coronary artery disease (CAD), 7.9% have congestive heart failure, 6.6% have stroke while more than a quarter of them 27.8% suffer from chronic kidney disease, almost a quarter 22.9% have foot problems and last but not least 18.9% have eye damage[4]. All these complications along with the metabolic deterioration demands a large amount of patient's every day energy, planning and thought[7], which leads to a situation called by Rubin[7] "diabetes overwelmus".

QUALITY OF LIFE

The reality is that diabetes influences patients' lives. The mere presence of diabetes deteriorates a person's quality of life (QoL). When diabetes coexists with other chronic illnesses the effect is even worse. But what exactly is QoL? Is it the mere absence of sickness in a man's life? Is it something more? Is it measurable? The worldwide interest is reflected on the 1950000 articles and reviews published the last five years on this research area while the numbers of publications on each diabetic complication are between 15000 and 28000 depending on the complication. Notably only one article was found to asses family functioning.

As Snoek *et al*[8] describes, we are not certain of the origin of the phrase QoL, but American economists Samuel Ordway (1953) and Fairfield Osborn (1954) are considered to be the first to have used the term. Others who used almost the same words was John Galbraith (1967), American president Lyndon B Johnson 1964 followed by social scientists in 1960's who were interested in the new topic of QoL, and particularly the correlation between markers of QoL (such as income level social interaction), and the way individuals perceive them το define their QoL. Surprisingly enough

biological health wasn't a determining factor. Because of the social progress and the medical development, research focused on the issue of well being as patients perceive it.

As Snoek *et al*[8] describes after World War Ⅱ and the introduction of new medicines, the numbers of patients with chronic diseases increased continually. In parallel there was a growing need for evaluation of treatments in terms of medical efficacy but also in terms of everyday life improvement as patients understood it[8]. No sooner than 1976 was the concept of QoL included in the *Index Medicus*[8]. By the year 2000, there had been over 300 articles on the issue of QoL in diabetic population.

In 1997, the World Health Organization (WHO) introduced the first definition of health as "A state of complete physical, mental, and social well-being not merely the absence of disease". WHO, furthermore, introduced QoL as an estimation of well-being as well as a the measurement of health and the effects of health care[9]. WHO defined QoL as individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Therefore, except for person's physical health definition of QoL includes psychological state, level of person's independence, social life and personal beliefs[9].

According to United States Centers for Disease Control and Prevention (CDC) QoL is a multidimensional concept that includes evaluations of both positive and negative aspects of a person's life. Since the 1980s, the term health-related quality of life (HRQoL) has comprised those aspects of QoL that can be shown to affect physical or mental health[10-13]. HRQoL includes physical and mental health perceptions (health conditions, social and socioeconomic status) and community-level resources, conditions (practices that influence health perceptions and functional status). According to the above, CDC has defined HRQoL as "an individual's or group's perceived physical and mental health over time"[10-13].

Undoubtedly the answer to the context of happiness and QoL is obscure and although there is no consensus among scientists, it is mostly agreed that QoL: (1) includes many different aspects as mentioned previously; and (2) should be measured through patients perception of well being or the lack of it in their lives[8]. Directly related and a crucial component of QoL is HRQoL. Many times the two concepts have been confused or thought to be identical, or synonymous to well-being, which of course is a mistake. During the last decades the researcher's interest has turned to the concept of disease specific QoL as a treatment goal[14] and important component of therapy. The whole philosophy of diabetes treatment has changed from physician-centered to patient-centered. The last ADA-EASD guidelines focus on patient participation in treatment options along with the physician. Concurrently HRQoL questionnaires have become important component of public health and are considered valid indicators of intervention outcomes and a powerful predictor of mortality and morbidity[15-18].

PSYCHOMETRIC TOOLS

Consequently, the necessity of developing special psychometric tools to measure HRQoL has risen rapidly. Thus, numerous such tools were developed, other generics and other disease specific in an attempt to determine the impact of diabetes and other chronic diseases, along with their complications on patient's lives and also the effect of medical interventions to the evolution of maladies. But as Snoek *et al*[8] states "there isn't a gold standard for the assessment of overall health related or diabetes specific QoL and efforts should be made towards the development of valid, reliable and user friendly assessment tools".

There are many psychometric tools developed in different languages which attempt to asses may aspects of diabetes interference with a person's life. The most used of the later or those which present a special interest are presented below.

The Diabetes Quality of Life Measure (DQOL) was introduced in the Diabetes Control and Complications Trial[19,20]. The scope was to assess four dimensions of diabetes impact: Satisfaction, treatment impact, anxiety for complications and social issues. The DQOL is widely used despite its limitations. Lower scores in this scale are associated with diabetic complications and glycemic control[19,21].

The Diabetes-Specific Quality of Life Scale (DSQOLS) has 64 questions has six dimensions: Social relations, leisure time restrictions and flexibility, physical complaints, worries about the future, diet restriction, and daily hassles. It is used only for type 1 diabetes and it is not validated in English[19,22].

The Diabetes Quality of Life Clinical Trial Questionnaire-Revised has 57 questions measuring physical function, energy, health distress, mental health, satisfaction, treatment satisfaction, treatment flexibility, and frequency of symptoms[19,23].

The Appraisal of Diabetes Scale has 7 questions focusing on diabetic patients' feelings and attitudes and the psychological effect of diabetes[19,24].

The ATT-39 and the revised ATT19 scale focus on the psychological adjustment to diabetes and diabetes integration which is not necessarily synonymous to diabetes specific HRQoL[19,25].

The Questionnaire on Stress in Patients with Diabetes-Revised has 8 dimensions: Leisure and work time, relationship with partner, with doctor, hypoglycemia, therapy, physical symptoms and anxiety about diabetic complications[19,26].

The Type 2 Diabetes Symptom Checklist is a 34-item scale assessing symptoms as hypoglycemic, cardiac, neuropathic, psychological, and vision-related. The scale covers a broad spectrum of symptoms which nevertheless can't always be attributed to diabetes.

The scale was developed in Dutch but there is English translation and validation[19,27].

The Problem Areas in Diabetes Scale (PAID-1) and the revised (PAID-2) are focusing on four dimensions: Overall emotional, interpersonal, treatment-related, and physician-related distress[19,28-30].

The Audit of Diabetes-Dependent Quality of Life (ADDQoL) has 15 questions measuring 13 life domains: Career, social life, family, friendships, sex life, leisure time opportunities, traveling, worries about the future, worries about the future for one's family and friends, and motivation to achieve things[19,31].

The widely used SF36 has 36 questions: An 8-scale profile of biological health and well-being scores as well as psychometrically-based physical and mental health measures and a preference-based health utility index. Physical function, pain, general and mental health, emotional and social function are assessed[32].

DIABETES AND HEALTH RELATED QOL

It is well-known that diabetes *per se*[33] causes a serious deterioration in general QoL mainly affecting the HRQoL. The outcomes are similar worldwide, varying in the grade of influence. Most importantly there are studies[34] implementing that the low QoL anxiety and depression of individuals who, aren't yet officially diagnosed for diabetes but who are at high risk for diabetes. Therefore, clinicians should be educated that high-risk patients at a prediabetic state might have decreased HRQoL and depression, a health dimension that should not be ignored[34].

As shown in a study in three different states in Malaysia there was a statistically important difference in QoL among the three studied populations Malaysian, Indian and Chinese[35]. The Chinese scored significantly lower (21.0 ± 4.3) in the Asian DQOL compared to Malays (81.4 ± 9.0) and Indians (81.5 ± 9.2). Moreover, Chinese scored significantly lower (21.0 ± 4.3) on the Asian DQOL (diet) score compared to Malays (22.8 ± 3.6) and Indians (22.5 ± 3.7). The only component different in a deeper analysis was the different perception of diet among ethnic groups[35]. In the same study, sexual dysfunction lead consistently to lower QoL (-10% in English speaking -5.9%, in Mandarin speaking Chinese, -6% in Malaysians traditional language speaking) in all sub groups whilst there were differences in other predictors. These findings are similar to a Singapore study by Wee *et al*[36] in 2005 which showed ethnicity as an important factor influencing QOL in people with diabetes[37].

In contrast to other studies, the surveys conducted in Nordic population[38] in primary health showed difference between impaired glucose tolerance and overt diabetics whilst the outcomes on HRQoL showed lower scores especially for type 2 diabetics in accordance with literature[39,40]. Older and poorer controlled patients showed lower scores. The most important factor in Nordic studies[38] for the deterioration of HRQoL was the presence of complications, especially CAD and non-vascular complication such as minor psychiatric disorders or musculoskeletal disorders. Nevertheless Viinamäki *et al*[41], found no increased rate of minor mental disorders among diabetic patients but when they coexisted the symptoms tended to be more severe. Furthermore, neuropathy was found to be a predictor of mental disorders in that study. Surprisingly microvascular complications did not have great effect in HRQoL. Other notable findings were that personalization and tailor suited therapy along with continuity in care[42-44] have promising results.

In a study[45], which started in the Cost of Diabetes Type 2 in Europe - (CODE-2) study, a Dutch population of 1371 type 2 diabetics was evaluated using EQ-5D and EuroQol VAS scores for HRQoL and Diabetes Treatment Satisfaction Questionnaire (DTSQ). The outcomes showed good correlation between EQ-5D and EuroQol Vas score although scores in one did not necessarily mean same scores in other. Lower scores were reported as age preceded more, in female sex, with obesity, with insulin use and as complications appeared. Especially low scores were observed for the combination of microvascular and macrovascular complications[45]. Notable points were that anxiety and depression increased and then decreased with age. An explanation given from the writers is that older people attribute their limitations to aging and cope or accept them better than younger people. Another explanation is that in younger populations the fear of future complications is greater. One more interesting point is that duration of diabetes isn't correlating with HRQoL as does not treatment satisfaction. The later is associated with the physician attitude towards the patient and the level of communication between them, fact consistent with literature[14]. The individuals with diabetic neuropathy had lower scores than those with foot ulcers. At last, questions were posed in term of EQ-5D responsiveness to change[45,46].

In another cross sectional study[47], conducted in United States, Self-Administered Quality of Well Being index (QWB-SA) was given to 2048 diabetics type 1 and type 2. Health scores were lower in women and obese patients, and in subjects with kidney disease and arterial hypertension. Scores were substantially lower in type 1 diabetic subjects with retinopathy, neuropathy, foot ulcers, amputation, stroke, and congestive heart failure. The highest scores among the subgroups had the group of diet controlled no obese diabetic men without microvascular, neuropathic, or cardiovascular complications. The same findings were observed in type 2 diabetics. At last, the authors implemented that there might be a correlation between lower than high school education and a deterioration of scores but the writers explained that the sample was inappropriate less than 7% and the chose not to comment on that variable.

Also similar were the findings of a study of diabetic population of a small isolated rural Canadian diabetic population in Bella Coola valley[48]. SF36 and BRFSS

(devised by the CDC, which aims to healthy/unhealthy days and limitations) were used and the scores were correlated to clinic chart information. Of note 57% of diabetic responded, whilst only 37% of non-diabetics. The sample was estimated as representative of the population of diabetics of the area and also in terms of complications CAD (16% *vs* 19%), retinopathy (15% *vs* 14%), cerebrovascular disease (9% *vs* 8%), neuropathy (9% *vs* 10%), peripheral vascular disease (7% *vs* 7%), and nephropathy (6% *vs* 7%). HRQoL scores were lower for diabetics. Factors related to health related QoL scores were duration of diabetes, insulin, and long-term complications of diabetes. Low HbA1c levels were paradoxically associated with lower QoL scores and there was an inverse relationship between duration of diabetes and QoL. The later is consistent with some studies[49] reporting the same outcomes while there are others reporting improvement with age[49-51].

Interestingly there were similar results in a recent review of the Iranian studies[52]. On the topic of the QoL in diabetic population, mostly type 2 and to smaller extend type 1diabetics. Women and older people had lower HRQoL than men and socioeconomic and marital status was positively associated with HRQoL. There were negative associations between HbA1c, BMI, blood pressure, lipids and HRQoL. Also deterioration of HRQoL was shown in the smokers group, whilst conflicting were the results concerning the duration of diabetes and the comparison of rural urban population. The writers note the methodological defaults of the studies. Nevertheless it is notable that the outcomes are consequent with the international studies although there is a difference in culture, diet and exercise habits.

In the UKPDS 37[53], study type 2 diabetics without any complication had a mean EQ-5D index value of 0.83, compared with 0.85 in a Norwegian study[54] conducted by mail in 2006. In the UKPDS 37 study the EQ-5D detected significant differences between people with and without complications In the UKPDS 37 study the EQ-5D detected significant differences between people with and without macrovascular complications, but not microvascular complications. In the same line, in a Singapore cross sectional study by Quah *et al*[55], used EQ5D and SF36 on 699 diabetics reported lower HRQoL in patients with symptomatic complications. This is consistent with many studies[53,56,57].

DIABETES COMPLICATION AND COMORBIDITIES

As seen in the referred above studies diabetes exercises its dark influence when complications start to make their presence in patients' lives. In a Chinese study involving type 2 diabetics[37], which was part of the JADE program Zhang *et al*[37], reported a mean EQ-5D index was 0.897 ± 0.173. Over 80% of diabetics had either hypertension or dyslipidemia and over half were obese. Nephropathy, neuropathy and CAD were associated with low EQ-5D index while retinopathy was not. Notably, hypertension was correlated with EQ-5D index. The outcomes were consistent with a Singapore study[58] while Dutch and Norwegian studies involving Caucasian populations[45,54] reported lower scores. In another Chinese study by Goh *et al*[35], in multiethnic environment diabetic complications had a great impact on QoL.

In the Norwegian study by Solli *et al*[54], patients with complications had reduced HRQoL; 0.90 for those with type 1 diabetes and 0.85 for those with type 2. Presence of one complication decreased scores to 0.76 and 0.80, respectively while with 2 or more diabetic complications the scores were 0.55 and 0.64, respectively. Cerebrovascular disease and neuropathy had a negative impact on overall HRQoL in both types of diabetes, while CAD had an impact on those with type 1 diabetes.

In the Dutch study by Redekop *et al*[45] in type 2 diabetics older patients, female subjects, treatment with insulin, obesity and presence of complications were correlated with a lower HRQoL. In the Canadian Bella Coola survey[48] the rates for diabetes complications regarding CAD (16%), retinopathy (15%), cerebrovascular accidents (9%), neuropathy (9%), peripheral vascular disease (7%), and nephropathy (6%). SF36 scores for diabetics were lower as follows: Physical functioning -13.7, in Social functioning -8.8, in bodily pain -11.1, in role physical -27.4 in role emotional -22, in mental health -3.5 in vitality -6.3, in general health -16.3. Diabetics had more unhealthy days when measured with Mean healthy/unhealthy day scores: +4.4 for unhealthy physical, +2.3 for unhealthy mental, +3.4 for limited by health, +5.4 for limited by pain, +1.9 for felt depressed, +3 for felt anxious, +2.6 for poor sleep, -1.3 for felt healthy. In an American study by Coffey *et al*[47], with 2048 type 1 and 2 diabetics. scores were lower (0.058-0.208) in type 1 diabetics with retinopathy, neuropathy, foot ulcers, amputation, stroke, and congestive heart failure. Health scores were significantly lower (0.052-0.170) in type 2 diabetics with retinopathy, end-stage kidney disease diabetic foot, neuropathy, stroke and heart failure[47]. Ragnarson Tennvall *et al*[59] also, assessed scores in subjects with diabetic foot problems using the EuroQol-EQ5D questionnaire. In this subgroup, major amputations (EQ5D: 0.31) and current foot ulcers (EQ5D: 0.44) were related with lower scores than primary healed ulcers (EQ5D: 0.60) or minor amputations (EQ5D: 0.61).

A Greek study[6] of elderly people living in rural place showed that the most important predictors of impaired HRQoL were female gender (55.4 in the SF36 psychometric tool), diabetic complications, comorbidities and diabetes duration. Older age (56.5 in the SF36 psychometric tool), lower education (60.5 in the SF36 psychometric tool), being unmarried (59.6 in the SF36 psychometric tool), obesity (60.5 in the SF36

psychometric tool), hypertension (62.7 in the SF36 psychometric tool) and dyslipidemia (58.8 in the SF36 psychometric tool) were also associated with impaired HRQoL. In an article of 2006 Piette *et al*[60] note: Most adults with diabetes have at least one comorbid chronic disease and as many as 40% have at least three. The authors categorize comorbidities into groups according to their clinical severity (end stage cancer or stage Ⅳ heart failure), the presence or absence of symptoms (dyslipidemia, hypertension *vs* rheumatoid arthritis) and their concordance or discordance to diabetes (dyslipidemia *vs* low back pain) without clearing the importance of the presence of comorbidities of each category to the evolution of diabetes. In other studies the coexistence of comorbidities resulted in lower scale scores. Also, lower HRQoL was reported in many studies assessing the co-existence of diabetes and other chronic diseases and co morbidities. In a study by Maddigan *et al*[61], the estimated score of diabetics with no complications was slightly lower than the general population, but when co morbidities added up in a patient's life the score deteriorated severely. Triplets of comorbidities were associated with HRQoL deficits. There are studies that correlate exercise with QoL reporting the highest level of physical activity in respondents with better HRQoL and overall health[55]. Wee *et al*[62] describes three possible types of correlation between diabetes and other medical conditions: (1) additive; (2) synergistic; and (3) subtractive relationship, while in his study reports the above mentioned correlation to be additive. He also reports diabetes in general as having moderate influence on subjects in comparison with other chronic illnesses. Another increasingly interesting but not so illuminated point is the interaction between comorbid chronic diseases, innovative treatments such as immunosuppressive agents and the development of overt diabetes to prior non diabetic patients as Pereiraa *et al*[63] high lightened. In this article the authors showed that CsA, tacrolimus and especially rapamycin affected lipolysis of human adipocytes through multiple metabolic pathways and regulations (IL6, TNF, inhibition of mTORC1 and 2 and consequent anomaly in the expression an stimulation of PPARγ) thus impairing the capacity of adipose tissue for plasma lipid clearance, which might contributes to dyslipidemia, fatty liver and promotes the onset of overt diabetes[63].

DEPRESSION, DEMENTIA AND DIABETES: AN INTERESTING TRIANGLE

The coexistence of depression and diabetes has drawn researchers' attention. The fact is quite justified since numerous studies have demonstrated the obscure effect of depression in the evolution of diabetes especially when comorbidities or complications exist[64-66]. Another less studied aspect is the effect of antidepressants on glucose metabolism. Some of them have shown diabetogenic action in non-diabetic depressed patients while others have proved to ameliorate glucose metabolism and consequently they are preferable for treatment of the diabetic population[67]. It is described that effective treatment with antidepressants improves glucose levels in nondiabetics. Cognitive behavioral therapy and selective serotonin reuptake inhibitor (SSRI) improve glycemic control, whereas noradrenergic antidepressants and tricyclic antidepressants cause alter metabolic control[67]. Further illumination on the extremely complex issue of interaction between depression treatment and the development and evolution of diabetes is derived from study of Köhler *et al*[68] who reports a beneficial outcome when statins (most of which is diabetogenic and a standard treatment of diabetic dyslipidemia) are added to SSRIS. The study of Goldney *et al*[64], showed increased prevalence of depression almost 24% of the diabetics compared with 17.1% of the non-diabetics. Also Gavard *et al*[69], in a systematic review of depression in diabetes provided the range of 8.5%-27.3% regarding the prevalence of depression in diabetics. On the other hand depression is related with a 60% increased risk of type 2 diabetes[70]. Goldney *et al*[64], gave an explanation through deterioration of recovery after a cardiac[71], malignancy survival, and predisposition to infection. Many pathways have been proposed for this dysfunctional immune system. The impact of depression on diet, exercise, smoking, alcohol abuse, compliance to treatment regimen. Regardless of the mechanism, the outcomes are clear about the negative role of depression on the course of the diabetes progression[66]. At last Lin *et al*[72], implements those patients with diabetes and coexisting depression are at increased risk. Some of those are infections, dementia, chronic obstructive pulmonary disease and arthritis. The new information emerging from the literature is the characterization of Alzheimer's disease as type 3 diabetes due to common metabolic paths, resistance to insulin and to similar deficits of brain nerve cell along with the improvement of brain cognitive function after intranasal insulin or peroxisome proliferator-activated receptor agonists[73-84]. Similar potential was demonstrated with incretin based therapies[85]. Needless to refer to what dementia does not only to a diabetic's QoL but life itself. To make it worse let us include what dementia does not only to the patient but also to spouses or family's life and QoL.

SOCIAL FUNCTION AND HRQOL

Apart from physical function mental and cognitive decline another aspect of diabetes gruesome influence on HRQoL takes place through the disintegration of the family. In a study by Takenaka *et al*[86], it was demonstrated that family issues were common among type 2 diabetics. The diabetic interacts with the family environment and social net (friends, relatives and acquaintances). Sometimes family acts like diabetes police and other times family doesn't want to participate to patients struggle for better glycemic control. Even

worse, they undermine patient's efforts. The patient reacts with aggressiveness, alienation, spite, or denial to comply, all of which leads to loss of social support, loss of belief in self-efficacy, poorer glycemic control, depression smoking, alcohol use and abuse, consequently complications and comorbidities and dramatic deterioration of HRQoL[73,84,87].

CAN DIABETES HRQOL BE IMPROVED?

Having processed all the above the international community is in search of the proper intervention for the fitting patient and specific divergence. Many studies have been performed and more of them are needed. It is well known the correlation between lifestyle interventions and better glycemic control, hypertension management and lipid management. There are many studies to confirm it[88,89]. In an analysis of 2004 by Ranji *et al*[90], many types of interventions are recognized: (1) provider reminders; (2) facilitated relay of clinical data to providers; (3) audit and feedback; (4) provider education; (5) patient education; (6) promotion of self-management; (7) patient reminders; (8) organizational change; and (9) financial, regulatory, or legislative incentives.

In the same analysis the writers identified as most common type of QoL intervention category of organizational change, followed by patient education and provider education. Moreover, it reports benefit of multifaceted interventions of disease management to a lesser extent and a no statistically significant benefit from the existence of a clinical information system.

Another review by Ricci-Cabello *et al*[91], aimed at quality of care of African Americans reported that interventions targeting self-management, education, reduced the percentage of HbA1c by 0.8%. No such relation was observed with interventions aiming at health care systems and multiple-target interventions

Whilst in a study of Wong *et al*[92], assessing the effect of education interventions among type 2 diabetics showed that there were no associations between the number of sessions attended and HRQoL. Another study evaluated HRQoL in overweight diabetic individuals after attending a weigh-lowering program. The evidence was that the diabetics had significant benefit especially those with the highest baseline BMI and the lower baseline scores[93].

At last a Norwegian review regarding diabetes interventions Sørensen *et al*[89], marked the need for multicomponent interventions targeting patients, health care professionals and policy makers. However, in the same review emphasize the fact that methods to assess the population based impact of these programs in the real world are limited. On the other hand, the outcomes of the Continuous Quality Improvement programme in Catalonia are encouraging and promising since they show the possibilities and potentials of health care interventions on diabetes HRQoL[94].

CONCLUSION

Diabetes continues to be a major contemporary epidemic. In addressing the challenges of confronting the epidemic a primary therapeutic goal is QoL. There is still a lot of confusion regarding the context of QoL, HRQoL and diabetes specific QoL. Recently numerous psychometric tools have been developed in the effort of evaluating QoL, HRQoL and Diabetes specific QoL. Diabetes affects major components of QoL although differences in terms of ethnicity, environment, gender socioeconomic status, culture, profession dietary and lifestyle habits do exist. More specifically: (1) the physical component especially with coexisting obesity complications as CAD renal failure, diabetic neuropathy or retinopathy or co morbidities; (2) the psychological component especially type 1 in younger subjects and in coexistence with depression; (3) the social component by destroying family ties and friendships; and (4) the mental cognitive component particularly when dementia presents.

In that scope numerous worldwide studies have been performed and have demonstrated little to moderate benefit in different components. Towards positive direction is the development of projects such as diabetes quality improvement project but there is al lot to be done in the future[32].

It would be ideal if the same psychometric tools could be translated validated and used in a worldwide scale in order to explore differences in the populations and extract comparable results. At last, diabetes is a strong and cunning enemy demanding all of our resources but technology development and the quality of unexplored yet human brain provide us with the insinuation of a brighter dawn in diabetes homeland.

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MINIREVIEWS

Syndecan-1-coating of interleukin-17-producing natural killer T cells provides a specific method for their visualization and analysis

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Abstract

Natural killer T cells (NKT cells) are innate-like T cells that acquire effector functions while developing in the thymus, polarize into three distinct functional subsets viz. NKT1, NKT2 and NKT17 cells that produce interferon (IFN)-γ, interleukin (IL)-4 and IL-17, respectively. However, there has been no unique surface markers that define each subsets, forcing investigators to use intracellular staining of transcription factors and cytokines in combination of surface markers to distinguish among these subsets. Intracellular staining, however, causes apoptosis and prevents subsequent utilization of NKT cells in functional *in vitro* and *in vivo* assays that require viable cells. This limitation has significantly impeded understanding the specific properties of each subset and their interactions with each other. Therefore, there has been fervent efforts to find a specific markers for each NKT cell subset. We have recently identified that syndecan-1 (SDC-1; CD138) as a specific surface marker of NKT17 cells. This discovery now allows visualization of NKT17 *in situ* and study of their peripheral tissue distribution, characteristics of their TCR and viable sorting for *in vitro* and *in vivo* analysis. In addition, it lays the ground working for investigating significance of SDC-1 expression on this particular subset in regulating their roles in host defense and glucose metabolism.

Key words: Natural killer T cell; NKT17; Syndecan-1 (CD138); Interleukin-17; Body fat

Core tip: Discrete subsets of innate-like Natural killer T (NKT) cells differentially produce three of the most potent and polarizing cytokines, interferon-γ (NKT1), interleukin (IL)-4 (NKT2) and IL-17 (NKT17). But very little is known about how the relationship among the functional subsets of NKT cells is regulated. A major obstacle was the absence of specific single surface markers that reliably identify each subset. Here we

highlight our discovery of syndecan-1 as a specific marker of NKT17 subset and its significance for understanding the role of NKT17 in glucose metabolism and autoimmunity.

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INTRODUCTION

We have recently published that syndecan-1 (SDC-1; CD138) is specifically expressed on the interleukin (IL)-17-producing subset of natural killer cells (NKT17) cells[1]. Briefly, we have previously shown that SDC-1 is expressed on double-negative T cells (DN T cells) that accumulate in lpr and gld mice[2]. After that we sought to know if SDC-1 express in innate cells and detected SDC-1 in a subset of NKT cells. We sorted and analyzed NKT cells subsets by genome-wide gene profiling using microarrays and identified SDC-1 is specifically expressed on the IL-17-producing subset of NKT17 cells[1]. Using SDC-1 expression on NKT17 cells, we visualized their development in the thymus, analyzed their tissue distribution. In addition, we sorted NKT17 cells, out distinguish them from interferon (IFN)-γ-producing NKT1 cells, we sorted each subset and study their characteristics *in vitro*. In this article, we briefly review SDC-1 expression on immune cells and highlight our results and speculate on the potential role of sdc1 in regulating homeostasis of NKT cells and the implication for glucose homeostasis and body fat development.

SDC-1

SDC-1 is a heparan sulfate proteoglycans that is predominantly expressed on epithelial cells[3,4]. It is composed of a short conserved cytoplasmic domain, a transmembrane domain, and a long variable ectodomain carrying heparan sulfate (HS) glycosaminoglycan chains[5]. Sometimes, SDC-1 used chondroitin/dermatan sulfate beside or instead of HS chains[6]. SDC-1 mediates its functions primarily by using HS chains to bind different ligands[7,8]. These include various growth factors such as fibroblast growth factors, Wnt, vascular endothelial growth factor, hepatocyte growth factor, cell matrix proteins, growth factors, cytokines, and chemokines[3,4] and their receptors[9-12]. Ligand binding to HS is regulated at the cell surface by two sulfatases (SULF-1 and SULF-2) and heparanases[13]. Number, position, and orientation of each sulfate group on HS chains play a role in dictating the ability of SDC-1 to bind ligands and initiate downstream signaling events[14-19]. These regulatory sequences have been proposed to act with both autocrine and paracrine mechanisms and represent potential novel targets for therapeutic interventions, particularly against cancer[12]. In addition, recent discoveries indicate that SDC-1 core proteins also has biological functions and can modulate cell behavior independent of HS. In contrast, the transmembrane and cytoplasmic domains of SDC-1 do not have intrinsic kinase or catalytic activity, but yet play important roles in signal transduction pathway by multimerization and/or interaction with other intracellular components, like GTPases or kinases[20]. This often happens in lipid rafts, which are enriched in glycosphingolipids and cholesterol[21] and essential for receptor binding and signal transduction from the cell surface into the cell. In addition, the short cytoplasmic domain of SDC-1 interacts with a number of cytosolic proteins and plays a role in endocytosis.

Using these various mechanisms, SDC-1 regulates multiple cellular functions, including cell proliferation, differentiation, and survival of adherent cells and tumors. Expression of SDC-1 is dysregulated in a number of cancers, including head and neck, ovarian, breast, and colorectal carcinomas[22]. In addition, SDC-1 has been implicated in regulating whole body energy metabolism in Drosophila[23] and body fat in mice[24]. Role of SDC-1 in cancers, infectious diseases, obesity, wound healing, and angiogenesis were reviewed recently[9,22,25] and hence will not be discussed in depth here.

Expression of SDC-1 in immune cells is limited and discrete

While ubiquitously expressed on epithelia and other adherent cells, expression of SDC-1 by the immune cells is limited to few cells as discussed below.

Expression in plasma and B cells: SDC-1 is a well known marker of plasma cells[3] and it has been reported on pre-B cells[26]. Other than that, SDC-1 is not known to be widely expressed among various normal immune cell types. SDC-1, however, is commonly expressed by myeloma cells and lymhopid malignancies and it has been implicated in survival, proliferation and metastasis of tumors[27]. But the exact roles of SDC-1 in the development and function of B cells and plasma cell remain poorly understood.

Specific expression of SDC-1 on NKT17 cells: Invariant NKT cells are highly conserved innate-like T cells that, unlike conventional T cells, are restricted to CD1d molecules and recognize glycolipids as antigens[28]. NKT cells acquire their effector functions while developing in the thymus[29] and differentiate into three distinct subsets that produce IFN-γ, IL-4 or IL-17 cytokine. These subsets were labelled in a manner typical to that of T helper cells (Th)1, (Th)2, and (Th17) cells[29,30]. Hence, the IFN-γ-producing subset is referred to as NKT1, the IL-4 producing subset as NKT2, and the subset that produces IL-17 as the NKT17 subset. Due to their innate nature, NKT cells rapidly produce copius amounts of these cytokines upon stimulation,

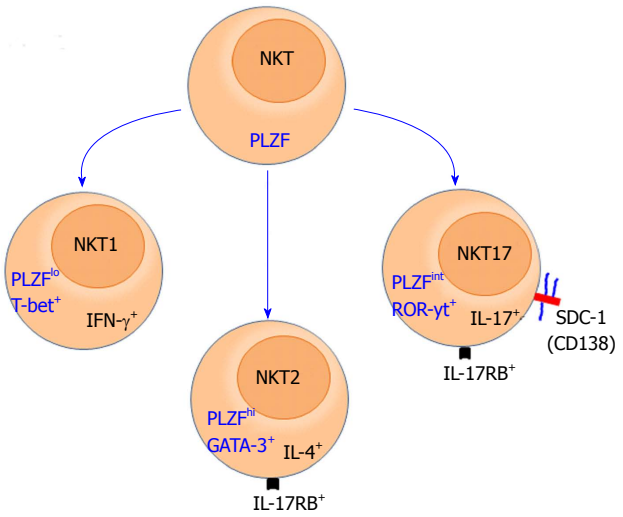

Figure 1 Surface expression of syndecan-1 specifically identifies Natural killer T 17 cells. The three functional subsets are currently distinguished from one another by intracellular staining for specific signature transcription factor or cytokine. Surface expression of SDC-1 can now be used for visualization and sorting of viable NKT17 cells. NKT: Natural killer T; SDC-1: Syndecan-1; IFN: Interferon; IL: Interleukin.

thereby playing critical roles in the initiation and shaping of adaptive immune responses[29,31,32]. These cytokines are highly potent and capable of polarizing adaptive immune responses into Th1, Th2 or Th17 type. Furthermore, because of the ability of these cytokines to inhibit each other function, the overall physiological functions of NKT cells and how the opposing functions of the three subsets are reconciled under physiological and pathological condition remain a mystery. Lack of progress in solving this paradox is rooted in the absence of reliable surface markers that identify and distinguish subsets of NKT cells from one another.

Currently, distinguishing among the NKT subsets is made using intracellular staining for signature transcription factors that control production of IFN-γ (Tbet), IL-4 (PLZF and GATA3), and IL-17 [retinoic acid-related orphan receptor γt (RORγt)][4,33]. Additionally, NKT subsets are identified based on intracellular staining for their signature cytokine, IFN-γ (NKT1), IL-4 (NKT2) and IL-17 (NKT17). Otherwise, It has been difficult to definitively distinguish among NKT cell subsets. Intracellular staining, however, requires fixation and permeabilization, which is a serious limitation that abroagtes the ability of investigators to do *in vitro* functional analysis using purified invidudual subsets. It has also impeded *in vivo* tracking and characterization of individual NKT cell subsets and full appreciation of the pathophysiologic functions of each subset. To avoid this problem, a combination of surface markers are currently used for this purpose, but they have their own shortcomings. For example, NKT17 cells can be identified based on low expression of NK1.1 and CD4, and high expression of CCR6 and IL17RB[34]. However, IL-17RB is also expressed by NKT2 cells and expression of NK1.1 is a strain-dependent and absent in most mouse strains[35]. Our recent identification of SDC-1 as a specific marker of NKT17 cells overcome this challenge at least for this subset[1] (Figure 1). This finding has been confirmed by three independent studies[36-38]. This discovery now allows visualization of NKT17 in the thymus and their peripheral tissue distribution, which is leading to novel insights into NKT cell biology.

Implication of SDC-1 expression on NKT17 cells on host defense and glucose metabolism

IL-17 is a potent proinflammatory cytokines that is required in host defense against infections[39] and been implicated in pathogenesis of asthma[40], and autoimmune diseases such as type 1 diabetes[41-43] and regulation of body fat[44]. In addition, IL-17 has been reported to modulate both adipogenesis and functions of adipocytes and glucose metabolism in mice[44,45]. Both IL-17AKO and IL-17RAKO mice has been reported to gain in weight due to the accumulation of visceral fat[44], suggesting involvement of IL-17 in maintaining body fat. NKT17 cells represent about 20% of NKT cells in the thymus[1] and approximately 2%-10% of total NKT cells in secondary lymphoid organs. NKT17 can secrete large amounts of IL-17 in response to various stimuli, such as infections, allergens, tissue injury and metabolic disorders[46,47].

Interestingly, NKT17 cells preferentially reside in visceral adipose tissue in mice[1] and their local and systemic frequencies are reduced in obese patients, suggesting their involvement in inflammation during obesity[48]. In addition, it has been reported that NKT17 could play a pathogenic role in the pathophysiology of diabetes[41]. Therefore, we speculate that studies addressing the roles of SDC-1 expressing NKT17 cell may provide an alternative approach to understanding its role in fat metabolism and glucose homeostasis. Thus, the findings by our group and subsequently other groups that NKT17 cells are identifiable by surface experssion SDC-1 is crucial for clear understanding of their biology and regulation and their physiologic role in thes steady state and disease condition[1,27,38]. For example, SDC-1 provides a unique opportunity for tracking and analysis of NKT17 cells *in vivo* and for sorting viable NKT17 for various *in vitro* functional studies and adoptive transfer experiments. In this regards, our findings of great responsiveness of NKT17 than do NKT1 cells is consistent with their preferential localization of NKT17 in white adipose tissue (WAT) and suggest special link to WAT.

CONCLUSION

The discovery of SDC-1 as specific marker for NKT17 cells laid the foundation for understanding the biology of NKT17 cells and their pathophysiologic functions. In addition, it will be helpful in uncovering specific markers for NKT1 and NKT2 by excluding NKT17 cells and sorting of pure NKT1 and NKT2 cells for gene expression profiling. Future studies are expected to develop into

understanding the significance of selective expression of SDC-1 by NKT17 cells and generating new information into the role of SDC-1 in the immune cells, which can lead to develoment of new strategies for manipulating individual subsets of NKT cells for therapeutic purposes.

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MINIREVIEWS

Osteomyelitis in diabetic foot: A comprehensive overview

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Abstract

Foot infection is a well recognized risk factor for major amputation in diabetic patients. The osteomyelitis is one of the most common expression of diabetic foot infection, being present approximately in present in 10%-15% of moderate and in 50% of severe infectious process. An early and accurate diagnosis is required to ensure a targeted treatment and reduce the risk of major amputation. The aim of this review is to report a complete overview about the management of diabetic foot osteomyelitis. Epidemiology, clinical aspects, diagnosis and treatment are widely described according to scientific reccomendations and our experience.

Key words: Diabetic foot ulcers; Diabetic foot infections; Osteomyelitis; Surgery; Antibiotic therapy

Core tip: Diabetic foot osteomyelitis is a current topic in the field of diabetic foot. Bone infection is a recognized risk factor for minor and major amputation. An accurate description about the diagnosis and treatment is useful to help physicians in the management of osteomyelitis in patients affected by diabetic foot ulcers.

Giurato L, Meloni M, Izzo V, Uccioli L. Osteomyelitis in diabetic foot: A comprehensive overview. *World J Diabetes* 2017; 8(4): 135-142 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i4/135.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i4.135

INTRODUCTION

Approximately 60% of diabetic foot ulcers (DFUs) are complicated by infection[1]. In more than two-thirds of the cases, infection is the main cause for major lower limb amputation in diabetic patients with foot ulceration[2-5]. Infections may complicate DFUs in both neuropathic and ischemic ulcers.

However, the simultaneous presence of peripheral arterial disease (PAD) and infection influence the evolution of DFUs, increasing the risk of non-healing and major amputation[1]. Therefore, in the case of diabetic foot infection (DFI) and limb ischemia, , it is mandatory an early performing revascularization to allow an

adequate blood flow in the area of the infection.

Even if a large variety of bacteria may colonize foot ulcers, infection is considered only if an inflammatory reaction develops due to the interaction between bacteria and host tissues. Colonization is usually limited to skin surface, while infection is generally characterized by the involvement of subcutaneous or deepest tissues. The severity of infection is related to location, depth (fascia, muscles, tendons, joints or bone), presence of necrosis and/or gangrene.

The diagnosis of infection is usually clinical while the microbiological characterization allows to detect the bacteria involved and drive the targeted antibiotic treatment.

Gram positive bacteria as staphylococcus aureus are the most involved in DFI. Nowadays, the resistance to antibiotics is increasing in diabetic population and multi-resistant organisms (MDRO) are common in DFI. Hospitalization, surgical procedures and long antibiotic therapy induce the development of MDRO or methicillin-resistant Staphylococcus aureus (MRSA)[6-8]. Osteomyelitis is a common DFUs infection, being present in 10%-15% of moderate and in 50% of severe infections[9]. The ulcers complicated by osteomyelitis often require surgical treatments and a long antibiotic therapy too[10-12].

Osteomyelitis is usually due to non-healing ulcers and it is associated with high risk of major amputation[13-15].

Diabetic foot osteomyelitis (DFO) is mostly the consequence of a soft tissue infection that spreads into the bone, involving the cortex first and then the marrow. The possible bone involvement should be suspected in all DFUs patients with infection clinical findings, in chronic wounds and in case of ulcer recurrence.

Osteomyelitis can affect any bone but most frequently the forefoot (90%), followed by the midfoot (5%) and the hindfoot (5%). Forefoot have a better prognosis than midfoot and hindfoot osteomyelitis. Above the ankle amputation risk is significantly higher for hindfoot (50%), than midfoot (18.5%) and forefoot (0.33%)[16-18]. An early and accurate diagnosis is required to ensure an effective treatment and reduce the risk of minor and major amputation[19,20].

THE MICROBIOLOGY OF OSTEOMYELITIS

The microorganisms involved in DFI show a various epidemiology depending on the characteristics of the patient, the clinical risk factors, the wounds (extension and depth) and the microenvironment.

The epidemiology of osteomyelitis reflects the one found in soft tissue infections, rarely mono-microbial and more often poly-microbial. *S. aureus* (up to 50% of cases), *S. epidermidis* (about 25%), *Streptococci* (about 30%) and *Enterobacteriaceae* (up to 40%) are the most commonly detected bacteria in DFO[21,22]. Among the Gram negative, *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus*, are the most common microorganism followed by *Pseudomonas aeruginosa*. The rate of anaerobes is usually low[21,22]. Also DFO show an increased MDRO mainly MRSA or extended-spectrum of beta-lactamase-producing[6-8]. The multi-drug resistance is a current topic for clinicians with significant influence on antibiotic approach.

DIAGNOSIS OF OSTEOMYELITIS

The diagnosis should be first based on clinical signs of infection supported by laboratory, microbiological and radiological evaluation. However, the diagnosis remains a challenge and DFO is often not recognized easily in its initial phase.

Infected wounds usually show purulent secretions or at least two signs of inflammation (swelling, erythema, blood serum secretion or simply blood with or without bone fragments)[14]. However, DFO can occur without any local sign of inflammation. Systemic symptoms such as fever and malaise are rare, especially in case of chronic osteomyelitis.

Various clinical findings can help clinicians in detecting bone infection. Two specific clinical signs are predictive of osteomyelitis. The first is the width and depth of the foot ulcer. An ulcer larger than 2 cm^2 has a sensitivity of 56% and a specificity of 92%. Deep ulcers (> 3 mm) are more easily associated with an underlying osteomyelitis than superficial ulcers (82% *vs* 33%)[23].

A second diagnostic criterion to detect DFO is the "probe-to-bone test" (PTB). PBT is performed probing the ulcer area with a sterile blunt probe. If the probe reaches the bone surface the PTB is considered positive. In a study involving 75 diabetic patients, PTB showed a sensitivity of 66%, a specificity of 85% and a positive predictive value of 89%[24]. The same test, evaluated in a subsequent prospective study of 1666 diabetic patients and compared with the culture of infected bones, was found to have a sensitivity of 87%, a specificity of 91%, a positive predictive value of only 57% and a negative predictive value of 98%[25].

Therefore, in the presence of infected ulcers, a positive PTB test is highly suggestive of osteomyelitis, but a negative test does not exclude it. Instead, in presence of an ulcer without clinical signs of infection, a positive test may be not specific for osteomyelitis while a negative PBT test should exclude a bone infection[26].

The combination of the PTB test with X-ray improve the sensitivity and specificity in the diagnosis of DFO[27,28]. Bone infection is also considered in case of visible or exposed bone or discharge of bone fragments (Figures 1 and 2).

Serum inflammatory markers as white blood cells (WBC), C-reactive protein, erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) are usually higher in DFO than soft-tissue infections. However, WBC and procalctitonin may be negative while ESR > 60 mm/h and/or CRP > 3.2 mg/dL in the presence of an ulcer deeper than > 3 mm are significantly predictive of DFO[29]. Furthermore, WBC, CRP and PCT values return to their normal range approximately in three weeks

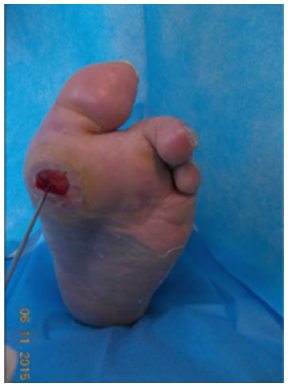

Figure 1 Positive probe-to-bone test for first metatarsal head.

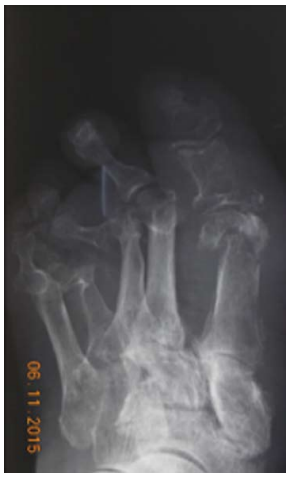

Figure 2 X-ray showing destruction of first metatarsal head.

after the treatment in both of soft-tissue and bone infection, while ESR usually remains high only in case of osteomyelitis[30].

Radiological tests are usually required to detect bone involvement in case of suspect osteomyelitis without clinical signs of infection, to confirm the clinical suspicion and detect the affected bone/bones and to distinguish DFO from soft tissue infection. X-ray is the first instrumental tool although it's arduous to detect the infectious process during the initial phase. Clear signs related to osteomyelitis are generally not evident until 30%-50% of the bone has not been involved; usually this condition happens after 2-3 wk. X-ray DFO imaging are usually characterized by osteopenia, erosion of cortical bone, cortical lysis, osteolysis, periosteal thickening, bone sequestration[31,32]. Radiological criteria of bone healing include: Well-organized consolidation of periosteum, reduction of bone lucency, reduction of pathological fractures related to bone infection, neo-formation of mineralized bone in the areas destroyed by the infection[33].

Scintigraphic examinations are more sensitive than X-ray, especially during the earliest stage of bone infection and the follow-up. However, the common limitation is the low specificity in the discrimination between

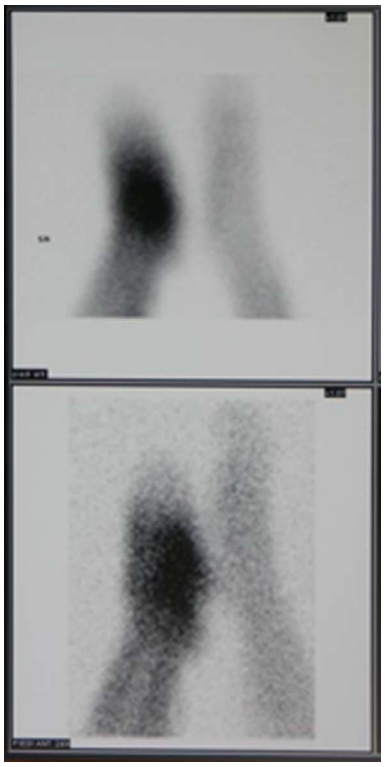

Figure 3 Leucocyte scan images showing area of increased uptake strongly suggestive of osteomyelitis in left mid and hindfoot.

soft tissues and bone infection[34]. The specificity of leucocyte scan is better than triple-phase bone scan even if the spatial resolution can be a limiting factor. However, labeled leukocyte imaging are more useful than bone scan for diagnosis, evaluation of bone affected and follow-up during medical treatment[35,36].

More recently, it has been shown that combined 99mTc white blood cell-labeled single-photon emission computed tomography and computed tomography (99mTc WBC labelled-SPECT/CT) imaging provide good spatial resolution with the three-dimensional CT-scan images and WBC uptake intensity yielding more information about the location and extension of infection[37,38]. Particularly, the role of 99mTc WBC labeled-SPECT/CT has been positively evaluated to identify the complete resolution of infection during the follow-up of patients treated by antibiotics[39] (Figure 3). The positron emission tomography-computed tomography (PET/CT) with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is an excellent hybrid imaging that can be used in the diagnosis of DFO and to distinguish bone from soft tissues infections. ^{18}F-FDG is a non-specific tracer to evaluate intracellular glucose metabolism; its uptake in increased in the areas of infection and inflammation[40-42] (Figure 4).

Magnetic resonance imaging (MRI) with gadolinium shows very high sensitivity (90%), and specificity (85%) in the diagnosis of DFO. The gadolinium uptake allows to distinguish between soft tissues and bone better than CT and scintigraphic methods[43,44]. The typical

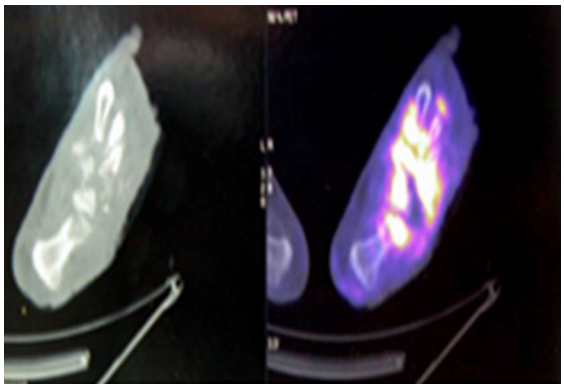

Figure 4 Positron emission tomography images demonstrating diffuse increased of 18F-2-fluoro-2-deoxy-D-glucose uptake of the right foot suggestive of severe osteomyelitis.

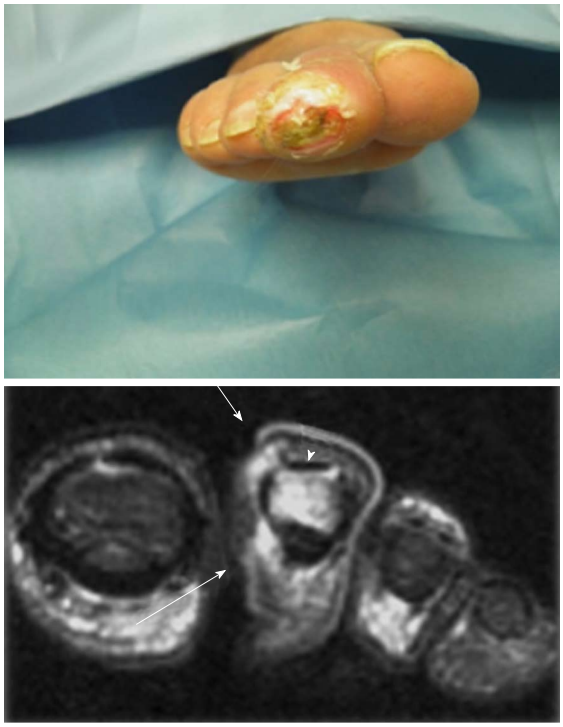

Figure 5 Osteomyelitis of second toe (distal phalanx) revealed by magnetic resonance imaging. The arrows and the arrowhead show the bone involvement of distal phalanx (second toe).

changes in the bone marrow predictive for osteomyelitis are low signal intensity on T1-weighted sequences and high signal intensity on T2-weighted sequences. These findings may be already evident 3 d after the onset of infection. The major limit is the reduced resolution in the evaluation of cortical bone that does not allow to highlight few cases of infection such as osteitis or to distinguish other causes of bone injury[45,46].

The guidelines suggest that the diagnosis of DFO include the combination of different diagnostic tests, such as PTB, serum inflammatory markers, X-ray, MRI or radionuclide scanning. X-ray should be always the first imaging evaluation; when more specific imaging are required, MRI is the first choice while white blood

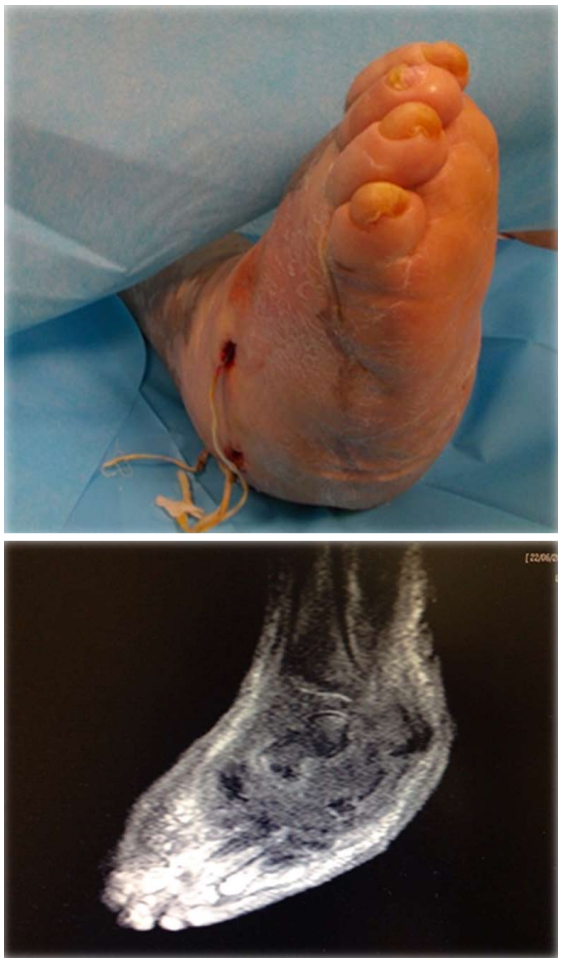

Figure 6 Severe osteomyelitis involving midfoot, hindfoot and ankle detected by magnetic resonance imaging.

cell-labelled radionuclide scan, SPECT/CT and ^{18}F-FDG PET/CT are used only if MRI is contraindicated[21,22] (Figures 5-7).

The gold standard for the diagnosis of osteomyelitis is the bone biopsy which provides histological and microbiological findings[21,22]. Histological criteria are: Bone erosion, marrow edema, fibrosis, necrosis, presence of inflammatory cells (both acute and chronic), seizure. Furthermore, the bone biopsy allows to identify precisely the bacteria involved in the infectious process and to evaluate the susceptibility to antibiotic therapy. The bone can be removed by a percutaneous approach through a not infected skin or during the open surgical procedures. In case of bone infection, superficial swab shows a low sensitivity, in fact a reliable correspondence between bacteria isolated form bone biopsy and swab culture is approximately of 38%[47]. Therefore, superficial swab should not be used in case of DFO. Bone biopsy is the most accurate test (preferably after 10 d of antibiotic suspension) even if in several cases it is not technically feasible. However, a recent study showed that the pathogens isolated from culture of deep tissues (removed from the area closest to the bone) are very similar to those obtained from bone biopsy (74.3% *vs* 82.8%)[48].

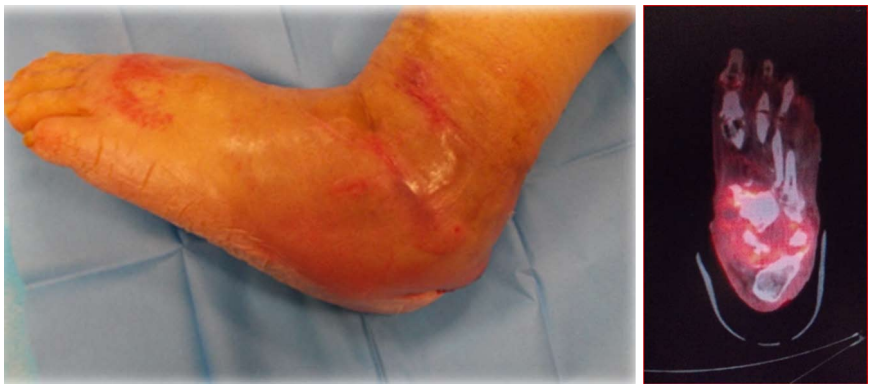

Figure 7 Severe osteomyelitis of forefoot, mid and hindfoot by positron emission tomography-computed tomography.

TREATMENT OF OSTEOMYELITIS

The treatment of DFO remains a hot topic in the field of diabetic foot. Over the years the most debated theories have been surgical or antibiotic therapy as first approach.

Nowadays the treatment of osteomyelitis is not completely standardized and evaluated case by case. Therefore, the guidelines broadly recommend the specific conditions for surgical or medical approach combined with conservative surgery. Conservative surgery means usually a procedure in which only the infected bone and the non-viable soft tissues are removed without any amputation[16].

Tan *et al*[49] have shown that an aggressive surgical approach with minor amputation reduces the risk of major amputation above the ankle and reduce the length of hospitalization and associated costs. The Authors report that forefoot amputation reduces the risk of major amputation in comparison to medical therapy performed for 3 d[49]. However, antibiotic therapy was performed only for 3 d and it is well known that DFO can require long antibiotic therapy.

Although an aggressive surgical approach could be mandatory under some circumstances, retrospective studies have shown that conservative treatment associated with prolonged antibiotic therapy is effective to promote wound healing and reduce the risk of major amputation and of ulcers recurrence[16,50,51].

Ha Van *et al*[50] have compared the conservative surgical treatment, defined as the resection of limited part of infected bone (phalanx and/or metatarsal head), associated with antibiotic therapy against antibiotic therapy alone. The conservative approach was more effective in terms of ulcer healing (78% *vs* 57%) and healing time (181 ± 30 d *vs* 462 ± 98 d, $P < 0.008$) compared to antibiotic therapy alone. Furthermore, the length of antibiotic therapy was significantly reduced in the group treated by conservative approach than the group treated by antibiotic alone (111 ± 121 d *vs* 246.9 ± 232 d, $P < 0.007$)[50].

Antibiotic therapy is widely used in association to surgical approach, both for minimal or extended procedures; however, several studies have reported many cases of DFO treated only by antibiotic therapy without surgery. Some Authors have reduced the role of surgery to treat bone infection, mainly in case of chronic osteomyelitis[52-54].

A recent prospective randomized clinical study has compared conservative surgery (removal of bone without amputation of any part of the foot) and antibiotic therapy alone. Severe infection, patients with PAD and severe co-morbidity were excluded. Osteomyelitis were located in the forefoot. The surgical group received empirical antibiotic therapy after the procedure. The group treated by antibiotics alone received for 90 d a targeted treatment according to the microbiological culture of deep soft tissues localized near the bone. The patient were followed for 12 mo after wound healing The rate of wound healing and healing time for respectively surgical and medical groups was similar (86.3% *vs* 75%) and (6 wk *vs* 7 wk). Only 16.6% of subjects treated by antibiotics alone required a secondary surgical approach. No patient received major amputation[55].

Also the optimal duration of antibiotic therapy is not completely defined. The Infectious Disease Society of America (IDSA) considers 4-6 wk adequate when the infected bone is not completely removed by surgery while at least 3 mo in case of antibiotic therapy alone[21]. However, the recent report of International Working Group of Diabetic Foot (IWGDF) suggested 6 wk of antibiotic therapy if the infected bone was not removed by surgery and no more than a week if infected bone was resected[22]. Lately, the aim is to reduce the duration of antibiotic therapy. In fact, prolonged use of antibiotics increases the risk of bacterial resistance, side effects and costs.

A prospective randomized study compared two groups of not ischemic patients with DFUs on the forefoot complicated by osteomyelitis treated with antibiotic therapy respectively for 6 or 12 wk. At the beginning antibiotic therapy was empirical and then driven by microbiological results. Sixty-six percent of patients resolved the osteomyelitis and there was not a significant difference between the two groups. Furthermore, the group treated for 12 wk showed more

side effects than the group treated for six weeks[56].

A significant aspect is to define the resolution of bone infection. Nowadays, there are no tests correlated to long-term resolution of osteomyelitis. The IWGDF suggest that a decrease of serum inflammatory markers, especially ESR, associated with the resolution of soft tissue infection, healing and positive evolution of radiological signs can be used to stop antibiotic therapy.

Chronic osteomyelitis is associated with a high percentage of recurrence despite a long antibiotic therapy. The rate of infection recurrence is approximately of 30%[31,54]. Recurrence might be related to the incomplete resection of infected bone or to resistant microorganisms persistently remaining in their biofilm[57]. The recurrence of DFO has to be considered in case of ulcer reappearance within 12 mo after the first healing. Furthermore, recurrent foot ulceration can promote the reappearance of bone infection. Adequate prevention is mandatory.

CRITICAL ISSUES

The appropriate management of DFO is closely based on both the severity of infection and patient's characteristics. Surgical and conservative approach shows advantages in some conditions and disadvantages in other. Several factors can influence the outcome. Among the advantages of surgical therapy there is the complete removal of the infected bone and the reduced duration of antibiotic therapy. On the other side an aggressive approach can lead to an extended tissue loss and it should be done only in patients with an adequate blood perfusion.

Further, the surgical treatment can impair the foot balance. In fact, a partial amputation (such as removal of a ray or a metatarsal head), mainly if associated to a pre-existing peripheral neuropathy, can increase biomechanical impairments of the foot and promote re-ulceration or new ulcerations in different areas.

Armstrong *et al*[58] have shown that forefoot amputation (toes or rays) reduces the joint mobility and increases the plantar pressures, 10-fold higher than that found in patients without forefoot amputation. Furthermore, increased peak pressure and limited joint mobility are significantly related high risk of re-amputation.

Molines-Barroso *et al*[59] analyzed the risk factors of re-ulceration in 119 diabetic patients who underwent resection of the metatarsal heads due to osteomyelitis. The rate of re-ulceration was higher in case of 1st and 3rd metatarsal head resection (69% and 52% respectively), followed by the resection of 2nd, 4th and 5th metatarsal head (44%, 25% and 19% respectively). The removal of more than one metatarsal heads was associated with a risk of re-ulceration approximately of 50%. The risk of ulceration transfer was significantly higher in case of 1st metatarsal head resection (P = 0.004)[59]. The main advantages of the medical treatment is to avoid the surgical treatment preserving the foot architecture and biomechanics.

The IDSA guidelines define the four clinical patterns where antibiotic therapy without surgery should be considered: (1) high risk of foot function loss in case of radical resection of infected bone; (2) severe deficiency in foot perfusion without chance of revascularization; (3) infection confined to the forefoot with only a minimal loss of soft tissue; and (4) excessive surgical risk according to patients general conditions. Furthermore, antibiotic therapy should be the first choice in case of small ulcers of the forefoot without bone exposure.

The main disadvantages of medical therapy may be the increased risk of infection recurrence, the long duration that can predispose to side effects and promote antibiotic resistance. According to IWGDF guidance, surgical bone resection is recommended in cases of bone exposure, progressive bone destruction and spreading of infection along the soft tissues[22].

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ORIGINAL ARTICLE

Basic Study

Insulin-mimetic compound hexaquis (benzylammonium) decavanadate is antilipolytic in human fat cells

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Abstract

AIM

To assess in rodent and human adipocytes the antilipolytic capacity of hexaquis(benzylammonium) decavanadate (B6V10), previously shown to exert antidiabetic effects in rodent models, such as lowering free fatty acids (FFA) and glucose circulating levels.

METHODS

Adipose tissue (AT) samples were obtained after informed consent from overweight women undergoing plastic surgery. Comparison of the effects of B6V10 and reference antilipolytic agents (insulin, benzylamine, vanadate) on the lipolytic activity was performed on adipocytes freshly isolated from rat, mouse and human AT. Glycerol release was measured using colorimetric assay as an index of lipolytic activity. The influence of B6V10 and reference agents on glucose transport into human fat cells was determined using the radiolabelled 2-deoxyglucose uptake assay.

RESULTS

In all the species studied, B6V10 exhibited a dose-dependent inhibition of adipocyte lipolysis when triglyceride breakdown was moderately enhanced by β-adrenergic receptor stimulation. B6V10 exerted on human adipocyte a maximal lipolysis inhibition of glycerol release that was stronger than that elicited by insulin. However, B6V10 did not inhibit basal and maximally stimulated lipolysis. When incubated at dose $\geqslant$ 10 μmol/L, B6V10 stimulated by twofold the glucose uptake in human fat cells, but - similarly to benzylamine - without reaching the maximal effect of insulin, while it reproduced one-half of the insulin-stimulation of lipogenesis in mouse fat cells.

CONCLUSION

B6V10 exerts insulin-like actions in adipocytes, including lipolysis inhibition and glucose transport activation. B6V10 may be useful in limiting lipotoxicity related to obesity and insulin resistance.

Key words: Adipocyte; Lipolysis; Amine oxidases; Insulin resistance; Obesity; Hydrogen peroxide; Vanadium; Antidiabetics

Core tip: This study investigates in murine and human adipocytes the antilipolytic properties of a conjugate of benzylamine and decavanadate (B6V10), already reported to lower hyperglycaemia in diabetic rodents. Data indicated that the conjugate dose-dependently inhibited submaximal activation of lipolysis in all the species studied. Such antilipolytic action deals with the *in vivo* FFA-lowering properties already described for B6V10 in diabetic rats. B6V10 also activated lipogenesis and glucose transport in fat cells. B6V10 should therefore be useful in preventing the lipotoxicity constituted by the unrestrained lipolytic activity of insulin-resistant adipocytes in obese individuals presenting type 2 diabetes, a state named diabesity.

Carpéné C, Garcia-Vicente S, Serrano M, Marti L, Belles C, Royo M, Galitzky J, Zorzano A, Testar X. Insulin-mimetic compound hexaquis (benzylammonium) decavanadate is antilipolytic in human fat cells. *World J Diabetes* 2017; 8(4): 143-153 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i4/143.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i4.143

INTRODUCTION

In obesity, the excessive enlargement of the adipose tissue (AT) is often associated with type 2 diabetes and morbid complications, especially when the hypertrophied fat depots are located in the intra-abdominal cavity (known as visceral fat). More than a decade ago, the links between fatness and altered glucose and lipid handling led to propose the term diabesity to define a complex disease distinct from "healthy" obesity[1]. The function of AT is not restricted to lipid storage: Indeed, it is also an endocrine organ, secreting numerous adipokines. Therefore, the excess of AT can be associated with insulin resistance[2,3], endocrine, metabolic and inflammatory disturbances, increasing the risk of co-morbidities, such as hypertension and dyslipidaemia. However, all these disorders, known as metabolic syndrome[4], not only co-exist with hypertrophied lipid storage but also with excessive lipid mobilization since the entire lipid turnover is dysregulated in diabesity. In fact, the circulating levels of the products of adipocyte lipolysis, namely free fatty acids (FFA) and glycerol, are dramatically elevated in obese individuals[5]. Such increase is likely resulting from a defective responsiveness of the adipocytes to the antilipolytic action of insulin. It is important to mention that insulin not only stimulates triglyceride synthesis, but also inhibits triglyceride breakdown, lowering basal lipolysis in fat cells and reducing FFA and glycerol blood levels. Therefore, in obese subjects with insulin resistance, the hypertrophied adipocytes release excessive amounts of FFA, which are not a good fuel supply to the other organs, and even hamper carbohydrate utilization. This contributes to maintaining

insulin resistance and its deleterious outcomes. Especially when occurring in visceral AT, such excessive lipolysis results in a high flux of FFA toward the liver, causing hepatosteatosis, inflammation, and worsening dyslipidemia. It is admitted that subjects with visceral fat have higher postprandial FFA and are at a higher risk of fatty liver disease and hepatic insulin resistance[6-8]. Indeed, clinical studies have demonstrated that the insulin resistance occurring in excessive AT affects metabolic parameters and increases liver damage[9]. Excessive FFA also have toxic effects in other organs (*e.g.,* alteration of insulin secretion in pancreas[10]), that contribute to exacerbate hyperinsulinemia and insulin resistance. At the cellular level, excessive FFA supply impairs mitochondrial function and leads to abnormal lipid oxidation, further disturbing lipid turnover and cell survival. All these effects of excessive FFA belong to a network of mechanisms currently defined as lipotoxicity[11].

Since unrestrained AT lipolysis results in increased fatty acid release, leading to lipotoxicity, the search for antilipolytic drugs has been re-considered recently as a promising approach to delay and/or reverse the onset of insulin resistance in diabesity. Consequently, many pharmacological agents are under investigation with the objective of reproducing and surpassing the beneficial effects of the classical antilipolytic agent Acipimox, reported to transiently alleviate insulin resistance in obese subjects[12]. Agonists of Gi-protein coupled receptors endowed with such antilipolytic properties have been reviewed elsewhere[5]. In this context, we aimed to verify in adipocytes the antilipolytic properties of a potential antidiabetic agent previously characterized as an insulin-mimicker on its basis to activate glucose transport in adipocytes from rodent models[13].

Our interest was therefore focused in searching how an arylalkylamine vanadium salt, endowed with insulin-like actions regarding glucose disposal[14], was able to directly reduce the lipolytic activity of freshly isolated adipocytes. Our previous studies showed that hexaquis(benzylammonium) decavanadate, the formula of which is $(C_7H_{10}N)_6V_{10}O_{28}.2H_2O$, is a salt conjugate of benzylamine and decavanate (B6V10) acting as a substrate for semicarbazide sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1)[15]. This enzyme is abundant at the surface of adipocytes and generates hydrogen peroxide when oxidizing its amine substrates. In the presence of B6V10, SSAO/VAP-1 also generated substantial amount of peroxovanadium, which, *via* phosphatase inhibition, was able to trigger insulin signalling downstream of the insulin receptor and to activate glucose transport in rodent adipocytes in the complete absence of insulin[16]. Chronic administration of B6V10 to rat or mouse models of diabetes substantially lowered blood glucose levels[13]. In addition, B6V10 normalized the plasma concentration of non-esterified fatty acids in severely diabetic rats[13]. Our present study consisted in a comparative approach testing under various conditions the putative antilipolytic actions of B6V10 in murine and human adipocytes.

We first tested increasing doses of B6V10 (0.1 to 100 μmol/L) on the triglyceride breakdown (lipolysis releasing FFA and glycerol) in rat adipocytes. Then a broader range of B6V10 doses (1 nmol/L to 100 μmol/L) was tested on the lipolytic and lipogenic responses of mouse adipocytes. Finally, our observations showed for the first time in human adipocytes a substantial antilipolytic action of supramicromolar doses of B6V10, which also activated glucose uptake.

MATERIALS AND METHODS

Patients and human adipocyte preparations

Adipocytes were isolated from samples of subcutaneous adipose tissue obtained from women undergoing abdominal lipectomy under the control of plastic surgery staff of Rangueil Hospital (Toulouse, France). A total of 13 overweight women (age range: 30-48 year, BMI = 25.9 ± 1.1 kg/m^2) were incorporated in the study following agreement of the INSERM guidelines and local ethic committee. The surgically removed pieces of human adipose tissue were placed in sterile plastic box, and transferred in less than one hour to the laboratory. The samples were immediately subjected to collagenase digestion at 37 ℃ to obtain freshly isolated adipose cells. To do so, pieces of adipose tissue were minced with scissors in Krebs-Ringer salt solution pH 7.5 containing 15 mmol/L sodium bicarbonate, 10 mmol/L HEPES and 3.5% of fat-depleted bovine serum albumin (KRBHA), and 5.5 mmol/L glucose. For the cell preparations used for glucose uptake assays, glucose was replaced by 2 mmol/L pyruvate. After digestion with 1 mg/mL collagenase type Ⅱ for approximately 45 min under agitation, buoyant adipocytes were separated by filtration through a 300 μmol/L mesh-screen and carefully washed in fresh medium to obtain adipocyte suspensions as previously described[17]. Final adipocyte suspensions averaged 14.5 ± 1.4 mg cell lipids/400 μL unless otherwise stated.

Rodent adipocyte preparations

The same procedure as above was applied for rat and mouse adipocyte preparations. A total of 10 male Wistar rats were purchased at Charles River (L'Arbresle, France) and were sacrificed according to INSERM guidelines for adipocyte preparation as previously reported[18]. Rat adipocytes were used at 15.3 ± 1.0 mg lipids/400 μL for the preliminary tests. Adipocytes were isolated from intra-abdominal adipose tissues obtained from male and female C57BL/6 mice. A total of 12 mice were used as already described[19] for the preparation of adipocyte suspensions that averaged 13.3 ± 0.8 mg cell lipids/400 μL.

Lipolytic activity assays

Filtration of digested adipose tissue, fat cell separation

and incubation were performed in disposable plastic wares at 37 ℃, as described[17]. All the tested agents were added to 400 μL of fat cell suspension in KRBHA under the form of 4 μL of a dilution extemporaneously done to reach the final indicated concentration. The agents were incubated with the fat cells at 37 ℃ under constant, gentle, shaking during 90 min. Incubations were stopped by placing the incubation tubes on ice. As already documented, lipolytic activity was determined by using glycerol release as an index[20], since FFA release follows parallel variations in our experimental conditions[21]. Once the buoyant adipocytes were frosted, 150 μL of medium were removed for glycerol spectrophotometric measurement at 340 nm, after addition of 1.5 mL of chromogenic mixture (0.6 mmol/L NAD, 1.4 mmol/L ATP, 0.2 mol/L glycine, 1 mol/L hydrazine, with 15 unit/mL glycerol phosphate dehydrogenase, and 0.6 unit/mL glycerokinase, pH 9.8), as previously described[22].

Glucose transport assay and de novo lipogenic activity

An isotopic dilution of [^{3}H]-2-deoxyglucose (2-DG) was added at a final concentration of 0.1 mmol/L (approximately 1300000 dpm/vial) to 400 μL of cell suspension after 45 min preincubation with the tested agents. Human fat cells were incubated for additional 10 min and then stopped with 100 μL of 100 μmol/L cytochalasin B. Aliquotes (200 μL) of shaken cell suspension were immediately centrifuged in microtubes containing dinonyl phthalate of density 0.98 g/mL, which allowed to separate the adipocytes as previously described[23]. The radiolabelled hexose internalized in viable fat cells (upper part of the tubes) was then counted in scintillation vials. The extracellular 2-DG present was determined using adipocytes whose transport activity was previously blocked by cytochalasin B at time 0. It did not exceed 1% of the maximum 2-DG uptake in the presence of insulin and was subtracted from the assays.

De novo lipogenic activity was determined by quantifying the D-[3-^{3}H]-glucose incorporation into lipids in mouse fat cells, according to[21]. They were incubated at 37 ℃ for 120 min in the same incubation medium as above, only containing only 0.6 mmol/L of isotopic glucose dilution as source of carbohydrates. The same vials were used for incubation, lipid extraction in an organic mixture for liquid scintillation (InstaFluorPlus) and counting of the labelled neo-synthesized lipids, following a procedure adapted from Moody *et al*[24].

Chemicals

Hexaquis(benzylammonium) decavanadate (B6V10) was synthesized and purified by Fernando Albericio and coworkers as previously detailed[16] and kindly given by Genmedica (Barcelona, Spain). Benzylamine, sodium orthovanadate, (-)-isoprenaline hydrochloride (isoproterenol), atrial natriuretic peptide (ANP), collagenase type Ⅱ and other reagents were from Sigma-Aldrich (Saint Quentin Fallavier, France). 2-DG and D-3-[^{3}H]-glucose were from Perkin Elmer (Boston, MA, United States).

Statistical analysis

Results are presented as means ± standard error of the means (SEM) of (n) observations. Statistical analysis for comparisons between B6V10 and respective control used Student's *t* test.

RESULTS

Effects of B6V10 in rat adipocytes

It is necessary to moderately activate lipolysis to detect whether a putative antilipolytic agent is able to limit triglyceride breakdown. This approach was first performed in rat adipocytes. The β-adrenergic agonist isoprenaline increased lipolytic activity in a typical concentration-dependent manner, and reached maximal activation at 1-10 μmmol/L. Addition of 100 μmmol/L of hexaquis(benzylammonium) decavanadate (B6V10) to increasing doses of isoprenaline impaired the β-adrenergic stimulation, clearly shifting the dose-response curve (Figure 1A). Noteworthy, the conjugate B6V10 did not alter the maximal effect of the highest isoprenaline dose. Similarly, the lowest dose of isoprenaline did not activate lipolysis sufficiently to allow any detection of B6V10 effect. Then, increasing concentrations of B6V10 were tested against an intermediate dose of isoprenaline (10 nmmol/L). In this condition, B6V10 dose-dependently inhibited the lipolytic activation induced by the β-agonist (Figure 1B). The conjugate therefore exhibited a clear and rapid antilipolytic effect in rat adipocytes, a cell model in which B6V10 has been already reported to mimic another insulin action: Glucose transport activation[13].

Effects of B6V10 in mouse adipocytes

Further studies performed on mouse adipocytes confirmed that increasing doses of B6V10 did not affect basal lipolysis, which was readily activated by isoprenaline (Figure 2A). Such lack of effect indicated that the conjugate was not lipolytic. However, other recognized antilipolytic agents, including insulin, were also unable to lower basal glycerol release (not shown). Consistent with our data obtained using rat adipocytes, activation of lipolytic activity was required to unmask putative antilipolytic effects. Consequently, B6V10 was tested at 1 μmmol/L in the presence of increasing doses of isoprenaline (Figure 2B). B6V10 did not impair the maximal lipolysis promoted by 0.1 and 1 μmmol/L of the β-adrenergic agonist, but it impaired the submaximal stimulation by 1 nmol/L and 10 nmol/L isoprenaline. When tested separately, the components of B6V10, benzylamine and sodium orthovanadate, did not alter the lipolytic effect of 10 nmol/L isoprenaline, while their combination at 100 μmol/L each was as antilipolytic as B6V10 (Figure 2B).

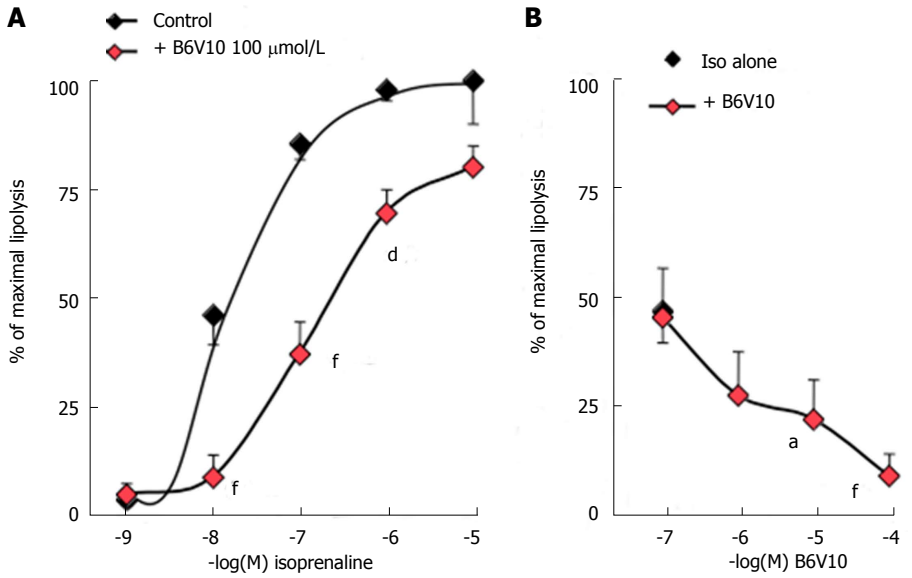

Figure 1 Influence of B6V10 on isoprenaline-induced lipolysis in rat adipocytes. Glycerol release was determined in rat fat cells incubated 90 min without (basal) and with increasing concentrations of isoprenaline alone (control, black symbols) or with the indicated doses of B6V10. Basal lipolysis (0.39 ± 0.06 μmol glycerol/100 mg lipid/90 min) was set at 0% while maximal lipolytic effect of 10 μmol/L isoprenaline (1.73 ± 0.14 μmol glycerol/100 mg lipid/90 min) was set at 100%. A: Antilipolytic effect of 100 μmol/L B6V10 (red diamonds) on dose-dependent activation by isoprenaline; B: Dose-dependent inhibition by B6V10 of the lipolysis induced by 10 nmol/L isoprenaline (iso alone). Mean ± SEM of 8-10 determinations. Significantly different from corresponding condition without B6V10 at: $^{a}P < 0.05$, $^{d}P < 0.01$, $^{f}P < 0.001$.

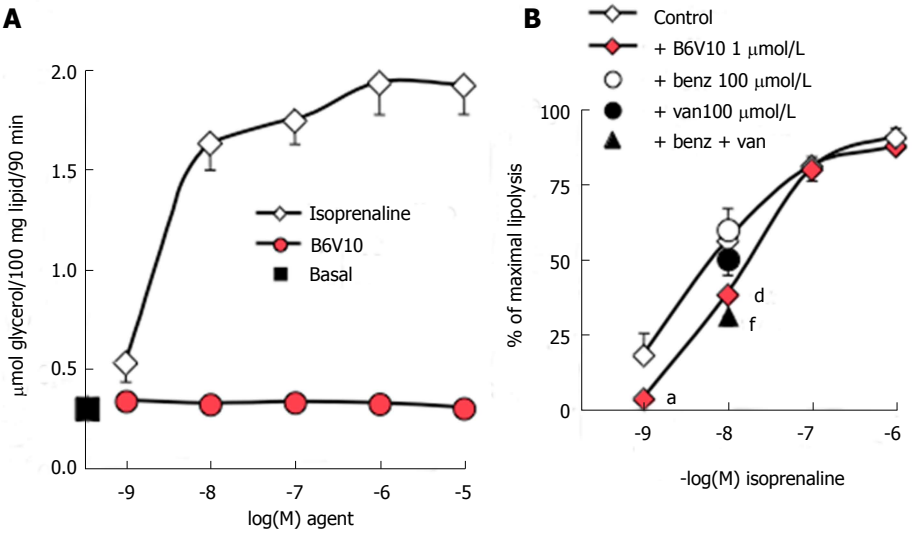

Figure 2 Influence of B6V10 on basal and isoprenaline-stimulated lipolysis in mouse adipocytes. Glycerol release was determined after 90-min incubation of mouse fat cells without (basal, closed square) or with the indicated concentrations of isoprenaline (open diamonds) or B6V10 (red symbols). A: Lack of lipolytic effect of increasing doses of B6V10 (red circles); B: Comparison of the inhibition of isoprenaline-stimulated lipolysis by 1 μmol/L B6V10 (red diamonds), 0.1 mmol/L benzylamine (open circle), 0.1 mmol/L vanadate (closed circle), or their combination (closed triangle). Mean ± SEM of 8 determinations. Significantly different from corresponding control at: $^{a}P < 0.05$, $^{d}P < 0.01$, $^{f}P < 0.001$.

Thus, the antilipolytic action of B6V10 was detectable only when lipolysis was mildly activated by the β-adrenergic agonist isoprenaline. This could suggest that B6V10 was acting by antagonizing activation of β-adrenergic receptors. To ascertain that an antagonism at β-adrenergic receptors was not mandatory to observe a response to the conjugate, we verified its direct effect on glucose utilization in mouse fat cells. When tested alone at 10 μmol/L, B6V10 reproduced 49.0% ± 7.8% of the *de novo* lipogenic action of 100 nmol/L insulin, which was equivalent to a threefold increase over the basal values of the incorporation of radiolabelled glucose into the lipids of mouse adipocytes (n = 5, not shown). At 100 μmol/L, B6V10 reached 85.0% ± 3.5% of the maximal lipogenic effect of insulin. These data supported that the conjugate was active *per se* on adipocytes through a mechanism distinct from antagonism at β-adrenoceptors, since these G-coupled receptors were not activated during the test of lipogenic activity. Moreover, this verification

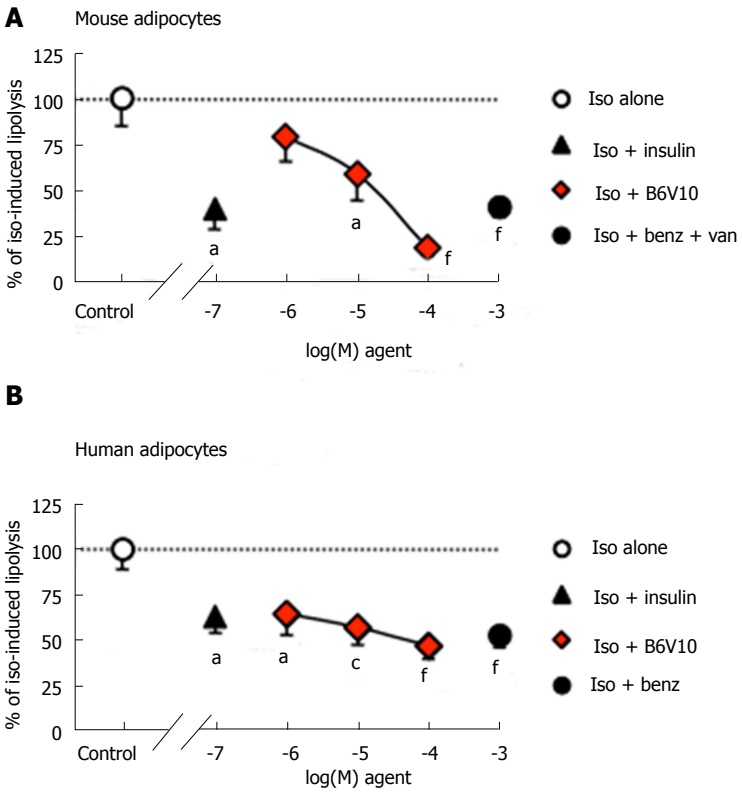

Figure 3 Comparison of the antilipolytic effects of B6V10 and insulin in mouse and human adipocytes. Lipolysis was activated by 10 nmol/L isoprenaline and considered as a control set at 100% (iso alone, dotted line) while basal was set at 0% in: Mouse adipocytes (A) or human adipocytes (B). The observed lipolytic response to the β-adrenergic agonist was significantly reduced in the presence of insulin (100 nmol/L, closed triangle), benzylamine (1 mmol/L alone for humans, or combined with 0.1 mmol/L vanadate for mouse adipocytes, closed circle), or increasing doses of B6V10 (1-100 μmol/L, red diamonds), at: $^{a}P < 0.05$, $^{c}P < 0.02$, $^{f}P < 0.01$. Mean ± SEM of 8 murine preparations (A) or 6-7 individual cases (B).

confirmed our previous characterization of B6V10 as an insulin-mimicking agent, acting through a hydrogen peroxide-dependent mechanism on the stimulation of glucose transport into fat cells[13]. In this context, the antilipolytic effect and the lipogenic effects of B6V10 could be considered as additional facets to the multiple B6V10 insulin-mimicking properties.

Translational studies on B6V10 antilipolytic action

Antilipolytic effects of insulin and B6V10 were then compared in mouse fat cells and in human adipocytes. In mouse, lipolysis was moderately activated by 10 nmol/L isoprenaline, reaching 1.28 ± 0.11 μmoles glycerol released/100 mg cell lipids/90 min. This sub-maximal stimulation of lipolysis represented an optimal condition to detect any putative induction or blockade by the tested agents. Figure 3 shows that the antilipolytic effect of a relatively high dose of insulin (100 nmol/L) was significant although incomplete. A similar partial antilipolytic effect was observed with 1 mmol/L benzylamine only in the presence of 0.1 mmol/L vanadate. The dose-dependent antilipolytic effect of B6V10 led to a stronger lipolysis inhibition than with insulin or benzylamine, at least when the conjugate was tested at 100 μmol/L (Figure 3A).

In freshly prepared human adipocyte suspensions, basal lipolysis was maximally activated by 10 μmol/L of isoprenaline (532% ± 107% of basal) but was unaltered by insulin alone (89% ± 16% of basal, n = 10, not shown). The stimulation of glycerol release by the dose of isoprenaline used in mice (10 nmol/L) was also submaximal. This dose triggered the production of 0.67 ± 0.08 μmol of glycerol/100 mg of cell lipids/90 min in human adipocyte preparations, while basal release was 0.20 ± 0.07 μmol glycerol/100 mg lipids/90 min. This lipolytic activation was considered as a 100% reference for testing the influence of insulin (100 nmol/L), benzylamine (1 mmol/L), or increasing doses of B6V10 (1-100 μmol/L) (Figure 3B). All these agents partially but significantly limited the β-adrenergic-induced lipolysis. When tested at 1 mmol/L, antilipolytic activity of benzylamine was as efficient as 100 μmol/L B6V10. The addition of vanadium did not enhance its effect (not shown).

B6V10 reduces submaximal but not basal and maximally-stimulated lipolysis in human adipocytes

Further analyses of the B6V10 antilipolytic effect were performed on human adipocytes and showed that 1 μmol/L of the conjugate could not impair the maximal lipolysis stimulation by 0.1, 1 or 10 μmol/L isoprenaline, while it impaired the submaximal β-adrenergic activation of glycerol release (Figure 4A). Similarly, no significant inhibition by B6V10 was detected on 1 nmol/L isoprenaline, when glycerol release values were close to basal levels. Moreover, B6V10 tended to limit the maximal effect of another strong lipolytic stimulator: The ANP, only active in human adipocytes[25,26] (Figure 4B).

In agreement with our data obtained in rodent adipocytes, micromolar doses of B6V10 were only limiting moderate lipolysis activation in human adipocytes. Thus, B6V10 appears to essentially hamper modest lipolytic activations, as those corresponding to the physiological modulation of triglyceride breakdown during interprandial cycles of energy supply and energy demand.

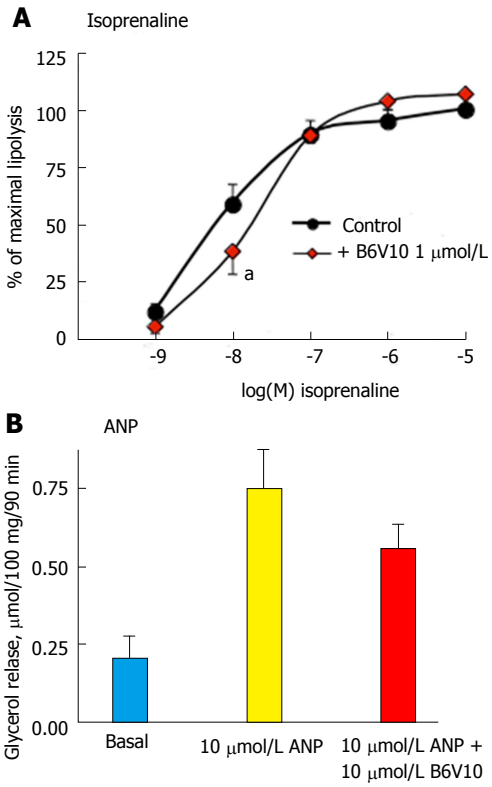

Figure 4 Antilipolytic action of B6V10 in human adipocytes depends on prior lipolytic activation. Lipolysis was activated by: Increasing doses of isoprenaline (A) or high dose of atrial natriuretic peptide (ANP) (B), and without or with the indicated doses of B6V10 (red symbols). Mean ± SEM of 6 determinations. Significantly different from corresponding condition without B6V10 at: $^{a}P < 0.05$.

Stimulation of glucose transport into human adipocytes by B6V10

Lastly, we explored whether the conjugate B6V10 could activate glucose transport in human adipocytes alongside its repression of triglyceride breakdown. In fact, previous studies that have demonstrated an insulin-like action of B6V10 on hexose uptake were restricted to murine adipocytes[13].

Here we show that freshly isolated human adipocyte preparations were highly sensitive to insulin, since 100 nmol/L of the hormone induced a four-fold increase in basal 2-deoxyglucose uptake (Figure 5). There was no significant effect of B6V10 on glucose uptake when added at inframicromolar doses. However, at 10 and 100 μmol/L, B6V10 reproduced approximately one third of the insulin stimulation of glucose transport, resulting in a highly significant activation. Sodium orthovanadate did not stimulate glucose uptake at 100 μmol/L and had no synergic effect with 10 or 100 μmol/L benzylamine. Indeed, when present at 0.1 mmol/L, benzylamine was as effective as 10 μmol/L B6V10 at stimulating hexose transport (Figure 5).

DISCUSSION

The property of B6V10, a conjugate of benzylamine and decavanadate, to lower blood glucose has been reported

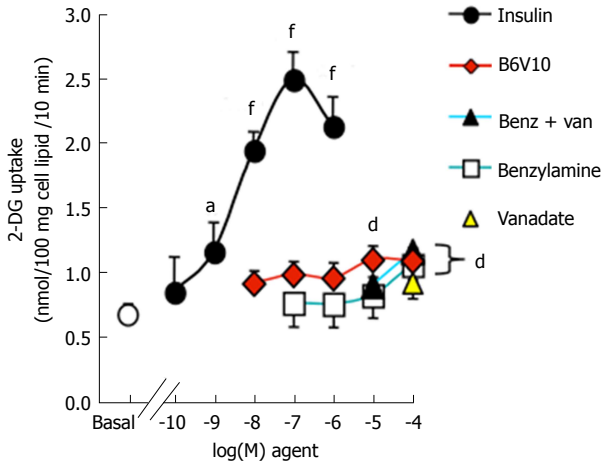

Figure 5 Activation of glucose transport in human adipocytes by supra-micromolar doses of B6V10. Suspensions of human fat cells (17 mg/400 μL) were incubated 45 min without (basal, open circle) or the indicated concentrations of insulin (closed circles), B6V10 (red diamonds), benzylamine (open squares), and 100 μmol/L vanadate alone (yellow triangle) or in combination with benzylamine (closed triangles), then [3H]-2-deoxyglucose uptake was assayed on 10-min period. Mean ± SEM of 10 adipocyte preparations. Significantly different from basal uptake at: $^{a}P < 0.05$, $^{d}P < 0.01$, $^{f}P < 0.001$.

together with *in vitro* demonstration of its ability to activate glucose transport and insulin signalling in adipocytes[13,14], while its ability to lower circulating FFAs in diabetic rats remains unexplained. Here we report for the first time that B6V10 is directly antilipolytic in murine and human adipocytes, a major finding regarding the growing interest for antilipolytic agents that may limit the harmful outcomes of lipotoxicity in diabesity[11,27,28]. Our observation using 1 μmol/L of the conjugate in human adipocytes, adds therefore a new insight to the development of vanadium-containing antidiabetic compounds, although it remains to avoid an overlap between their therapeutic and toxic doses. Accordingly, we are discussing below about the interest of inhibiting adipocyte lipolysis to reduce lipotoxicity, and about the possibility to develop vanadium-containing antidiabetic and anti-obesity agents that could become "drugable", two issues independently covered in very recent reviews[5,29].

In diabesity, when AT has developed an insulin resistance, the fatty acid storage in hypertrophied adipocytes under the form of triglycerides becomes limited due to a decrease in lipogenic and antilipolytic action of insulin. Such reduced insulin responsiveness derepresses lipolysis in adipocytes and leads to ectopic FFA deposition (in liver, vessels, muscles, endocrine glands), which in turn hampers glucose utilization and lipid oxidation in all these organs. To combat this lipotoxicity, there is a need to control excessive FFA mobilization from AT that requires the characterization of potent antilipolytic factors and constitutes a novel therapeutic approach for the treatment of obesity complications. In fact, there is mounting evidence that antilipolytic agents limiting the release of non-esterified fatty acid and glycerol into the blood stream, should be

considered as antidiabetic or anti-obesity agents[5]. In this regard, the reversal of lipotoxicity is proposed to contribute to the beneficial effects of old drugs, such as pioglitazone. These "novel" properties are added to the anti-inflammatory properties of pioglitazone that improve metabolic and secretory functions in adipocytes and β-cells[27], and lead to re-examine this old antihyperglycemic agent as a treatment for non-alcoholic fatty liver disease (NAFLD) that often complicates type 2 diabetes[28]. It is important to note that lipotoxicity can lead to severe NAFLD even when insulin resistance in AT is not concomitant with obesity. Indeed, the transgenic mice carrying fat-specific knockout of the insulin receptor are characterized by severe atrophy of fat depots, pronounced diabetes, and marked fatty liver disease[30]. Thus, it seems safer to limit ectopic lipid deposition by restricting excessive FFA release and blunting insulin resistance in adipocytes, even at the expense of maintaining adipose mass, than to overstimulate fat store mobilization. One has to keep in mind that one of the most powerful lipolytic agents, TNF-α, does not help in mitigating the deleterious outcomes of insulin resistance: On the opposite, it strongly desensitizes to insulin action and promotes inflammation.

Since we previously reported that chronic treatment with B6V10 lowered plasma FFA in diabetic rats[13], we asked whether this agent could be effective in lowering adipocyte lipolysis. In this comparative work, we brought compelling evidence that the conjugate inhibits lipolysis in rodent adipocytes with an efficiency greater than the ones obtained with its components used separately (benzylamine and decavanadate). Indeed, we have previously characterized B6V10 as an agent that exerts in adipocytes potent insulin-mimetic effects downstream the insulin receptor, in a manner that is sensitive to SSAO/VAP-1 inhibition and which reproduces the synergism between benzylamine and vanadate[13,14]. The effective doses of B6V10 in inhibiting lipolysis in rodent adipocytes are superimposable to those necessary for glucose transport stimulation. Moreover, our *de novo* lipogenesis experiments add to the list of B6V10 insulin-like effects[14] its capacity to activate glucose incorporation into the neosynthesized lipids in mouse adipocytes.

The fact that B6V10 was unable to impair maximal activation of lipolysis in all the models studied is not a concern since the amplitude of increased lipolytic activity of adipocytes is much lower in pathological states of insulin resistance than the activation that physiologically emerges during prolonged fasting or cold exposure[31]. Noteworthy, human adipocytes exhibited both lipolysis inhibition and glucose uptake activation in response to B6V10. Our data clearly show that the *in vitro* antilipolytic effect of a relatively high dose of insulin was not complete in subcutaneous adipocytes of sedentary women. Since insulin inhibited only by one-third of the response to isoprenaline, and since this effect was fully reproduced by 1 μmol/L of B6V10 (*i.e.,* at a dose only tenfold higher than that necessary for insulin), the conjugate can be definitely considered as a good insulin mimicker. Increasing the dose of B6V10 up to 100 μmol/L resulted in a higher but partial inhibition of lipolysis. Therefore, B6V10 could surpass insulin-like antilipolytic action in adipocytes from overweight subjects, who exhibited weak insulin sensitivity, although being non-obese and non-diabetic. Yet, the insulin antilipolytic response appeared to be more altered in these individuals than the insulin activation of glucose transport. The latter reached a four-fold stimulation of basal uptake in our conditions, which does not denote a fully developed insulin-resistant state for human fat cells[32]. Describing the exact onset of these defects was not in the scope of our studies, but deserves to be performed in future clinical studies, taking into account the influence of gender and fat depot anatomical location. Actually, it can be noticed that the maximal antilipolytic response to B6V10 was lower in human adipocytes than in rat and mouse models.

B6V10 is one of the promising antihyperglycaemic agents belonging to the wide family of vanadium derivatives. It can be summarized that, once ingested, vanadium is found in the organism under a cationic (vanadyl) or anionic (vanadate) form, the latter resembling to a phosphate group. In fact, orthovanadate ($H_2VO_4^-$) interacts with a pleiad of cellular components interacting with $H_2PO_4^-$, *e.g.,* enzymes influenced by (de)phosphorylation state. Yet, the ability of vanadium to mimic insulin actions in rat adipocytes has been reported in the 80s and univocally confirmed in all the insulin-sensitive tissues expressing GLUT4. Furthermore, we observed that vanadate and vanadyl were equally efficient in totally inhibiting rat adipocyte lipolysis at 1 mmol/L[33]. The current issue of vanadium pharmacology is to take advantage of these insulin-like properties without the concerns raised by the high degree of vanadium toxicity (due to accumulation in tissues like the kidneys and bones); in other terms: Lowering the risk/benefit ratio[29]. Among the various improvements raised by studies of chemico-biological interactions of vanadium derivatives[34], the vanadium peroxides, or pervanadates, formed by mixing vanadium and H_2O_2[16], have shown an increase in the potency for insulinomimetic actions in adipocytes[29]. With pervanadates, the effective doses were lowered from millimolar to micromolar range, as they are irreversible inhibitors of various phosphatases and act on target cells at much lower doses than vanadate. Recently, we synthesized and characterized salts composed by arylalkylamines combined with decavanadate that permitted to lower the effective antidiabetic dose of vanadium to non-toxic levels. The more active compound of this series, namely B6V10, mixes decavanadate, a complex form that increases adipocyte glucose uptake more potently than other vanadium forms[35], with benzylamine, also behaving as an insulin mimicker in human fat cells[36]. These two halves were already described to act synergistically, especially in fat cells where benzylamine is oxidized by the highly expressed SSAO/VAP-1,

thereby generating hydrogen peroxide[37], which in turn reacts with vanadate to generate peroxovanadate. This compound then inhibits protein tyrosine phosphatases and triggers glucose carrier translocation and hexose transport activation[38]. This cascade of events results in a substantial antihyperglycaemic action in diabetic rodents that is more potent than the separate effects of benzylamine and vanadate[39]. All these insulin-like actions disappear when SSAO/VAP-1 is pharmacologically inhibited or genetically invalidated[40]. Thus, when B6V10 undergoes oxidation by SSAO/VAP-1, it generates peroxovanadate and acts *in vitro*[16] as well as *in vivo*[14] to trigger antidiabetic actions. By releasing the real active vanadium-based ligands that interact with phosphatases near the target cells, the B6V10 is therefore a mean to improve decavanate "speciation" (see review from Scior and coworkers for further details[29]) and to circumvent the concerns raised by decavanadate toxicology[41].

Our *in vitro* analysis reveals a potent antilipolytic action of B6V10, which might be helpful in combating the lipotoxicity that participates to diabesity complications. Several concerns to this therapeutic potential could be raised since our experiments were performed only in adipocytes isolated from subcutaneous abdominal depots of overweight women.

The first concern could be the relevance of our observations for visceral adipocytes from massively obese subjects, considered as more harmful. Indeed, clinical studies have demonstrated that impaired triglyceride storage also occurs in the subcutaneous AT of insulin-resistant individuals when compared to their BMI-matched controls classified as insulin-sensitive[42]. Using deuterated water prolonged administration and functional exploration of subcutaneous AT, these studies elegantly indicated that, during the onset of type 2 diabetes in humans, there was a clear defect in insulin suppression of lipolysis and activation of *de novo* lipogenesis in the subcutaneous adipocytes themselves.

A second concern could be raised regarding the fact that we have only determined glycerol release as an index of lipolysis, while lipotoxicity is mainly supported by excessive FFA release. Previous studies on AT lipolysis and insulin sensitivity have evidenced a tight relationship between spontaneous glycerol production by human AT explants and insulin resistance in a large cohort of subjects presenting a wide range of BMI[43]. According to Girousse *et al*[43], both lipolysis end-products, glycerol and FFAs, were equivalent to show that partial inhibition of AT lipolysis improves insulin sensitivity[43].

Another limitation regarding the maximal antilipolytic capacity of B6V10 is that it is not complete and can be surpassed by various stronger antilipolytic agents (such as nicotinic acid, purinergic or α_2-adrenergic agonists, see[32]). However, these agents are unable to activate glucose uptake in human adipocytes (C. Carpéné unpublished observations) and do not offer the dual interest of B6V10 to lower both circulating glucose and lipids.

Lastly, insulin also plays lipogenic and antilipolytic actions when infused into the hypothalamus of rats[44]. Whether B6V10 also mimics insulin actions in the brain, in a manner that could influence its antidiabetic and lipid-lowering action during chronic treatment remains unknown and deserves further *in vivo* studies in insulin-resistant models.

Though being clearly antilipolytic in human adipocytes, 1 μmol/L B6V10 was not more effective than 1 mmol/L benzylamine, and the combination of vanadate with benzylamine did not lead to the synergism found in rat adipocytes. Indeed, in human AT, the maximal antilipolytic effect of B6V10 was comparable to that of benzylamine, already described to hamper about one-half of stimulated lipolysis[36]. Regarding the glucose uptake in human adipocytes, B6V10 is clearly stimulating, but there is no synergism between its components, benzylamine and vanadate, each one reproducing at 100 μmol/L the effect of 10 μmol/L conjugate. This is in apparent agreement with the proposed lack of glucose transport activation by decavanadate in human adipocytes[35], and confirms the absence of potentiation between SSAO/VAP-1 substrates and vanadium regarding glucose transport in human adipocytes[33]. Therefore, while noticeable synergism between SSAO/VAP-1 substrates and decavanadate occurs when using B6V10 in murine adipocytes, this apparently does not work as well in human fat cells, for a reason that remains to be elucidated.

Consequently, our comparative approach indicates that B6V10 cannot be immediately considered for clinical application as an efficient mean to increase the benefit/risk ratio of vanadium regarding its therapeutic antidiabetic indication. Nevertheless, it must be noted that, although B6V10 is not the most potent and powerful antilipolytic agents described so far in human adipocytes, it combines two insulin-like actions: Limiting lipolysis and increasing glucose uptake. In this regard, it should be considered as a valuable candidate to further develop an approach based on the mitigation of lipotoxicity in diabesity. This adds an alternative to classical antilipolytic agents proposed to limit lipotoxicity, such as nicotinic acid (Acipimox)[12], or lipase inhibitors[5]. Another consequence of our depicted interspecies differences is that the exploration of the antilipolytic properties in human adipose cells deserves to be applied to other vanadium conjugates recently tested with success on diabetic rodents, such as those combining metformin and decavanadate[45].

In conclusion, the conjugate of benzylamine and decavanadate B6V10 exerts insulin-like actions in human adipocytes, including lipolysis inhibition and glucose transport activation.

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COMMENTS

Background

Insulin resistance of adipocytes in hypertrophied fat depots leads to an increased lipolytic activity releasing in the circulation excessive amounts of free fatty acids (FFA) that accumulates under the form of triglyceride-rich ectopic lipid droplets in liver and muscles. The conjugate salt hexaquis(benzylammonium) decavanadate has been reported to lower circulating glucose and FFA in diabetic rodents, but its direct action of adipocyte lipolytic activity has never been assessed.

Research frontiers

This *in vitro* approach definitely brings evidence that B6V10 reproduces the rapid antilipolytic action of insulin in murine and human fat cells. At 100 μmol/L, B6V10 even surpasses the maximal inhibition of lipolysis induced by the pancreatic hormone. Since the molecule also stimulates glucose uptake in human adipocytes and has been demonstrated to exert antihyperglycemic actions in murine models of diabetes, it can be qualified as insulin mimicker.

Innovations and breakthroughs

In vitro, B6V10 exerts various insulin-like actions in human adipocytes including lipolysis inhibition and glucose uptake activation. This conjugate salt of benzylamine and decavanadate has the potential to alleviate the deleterious complications linked to the insulin resistance of adipocyte antilipolytic/lipogenic activities emerging in morbid obese and diabetic patients, and could be considered as a potential antidiabetic agent.

Applications

B6V10 could be useful as an auxiliary therapy in limiting the lipotoxicity related to obesity and insulin resistance. Its chronic administration might delay ectopic fat deposition and should reduce hepatic steatosis whether active in obese patients at doses acting in fat stores without exerting adverse effects elsewhere in the organism.

Terminology

ANP: Atrial natriuretic peptide; AT: Adipose tissue; BMI: Body mass index; B6V10: Hexaquis(benzylammonium) decavanadate; FFA: Free fatty acids; GLUT4: Insulin-sensitive glucose transporter; H_2O_2: Hydrogen peroxide; SEM: Standard error of the mean; SSAO/VAP-1: Semicarbazide-sensitive amine oxidase, identical to VAP-1 (vascular adhesion protein-1).

Peer-review

Manuscript presents solid data and is of good quality.

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ORIGINAL ARTICLE

Observational Study

Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study

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Abstract

AIM

To determine the short-term biochemical effects and clinical tolerability of intermittent fasting (IF) in adults with type 2 diabetes mellitus (T2DM).

METHODS

We describe a three-phase observational study (baseline 2 wk, intervention 2 wk, follow-up 2 wk) designed to determine the clinical, biochemical, and tolerability of IF in community-dwelling volunteer adults with T2DM. Biochemical, anthropometric, and physical activity measurements (using the Yale Physical Activity Survey) were taken at the end of each phase. Participants reported morning, afternoon and evening self-monitored blood glucose (SMBG) and fasting duration on a daily basis throughout all study stages, in addition to completing a remote food photography diary three times within each study phase. Fasting blood samples were collected on the final days of each study phase.

RESULTS

At baseline, the ten participants had a confirmed diagnosis of T2DM and were all taking metformin, and on average were obese [mean body mass index (BMI) 36.90 kg/m^2]. We report here that a short-term period

of IF in a small group of individuals with T2DM led to significant group decreases in weight (-1.395 kg, P = 0.009), BMI (-0.517, P = 0.013), and at-target morning glucose (SMBG). Although not a study requirement, all participants preferentially chose eating hours starting in the midafternoon. There was a significant increase (P < 0.001) in daily hours fasted in the IF phase (+5.22 h), although few attained the 18-20 h fasting goal (mean 16.82 ± 1.18). The increased fasting duration improved at-goal (< 7.0 mmol/L) morning SMBG to 34.1%, from a baseline of 13.8%. Ordinal Logistic Regression models revealed a positive relationship between the increase in hours fasted and fasting glucose reaching target values (χ^2 likelihood ratio = 8.36, P = 0.004) but not for afternoon or evening SMBG (all P > 0.1). Postprandial SMBGs were also improved during the IF phase, with 60.5% readings below 9.05 mmol/L, compared to 52.6% at baseline, and with less glucose variation. Neither insulin resistance (HOMA-IR), nor inflammatory markers (C-reactive protein) normalized during the IF phase. IF led to an overall spontaneous decrease in caloric intake as measured by food photography (Remote Food Photography Method). The data demonstrated discernable trends during IF for lower energy, carbohydrate, and fat intake when compared to baseline. Physical activity, collected by a standardized measurement tool (Yale Physical Activity Survey), increased during the intervention phase and subsequently decreased in the follow-up phase. IF was well tolerated in the majority of individuals with 6/10 participants stating they would continue with the IF regimen after the completion of the study, in a full or modified capacity (*i.e.*, every other day or reduced fasting hours).

CONCLUSION

The results from this pilot study indicate that short-term daily IF may be a safe, tolerable, dietary intervention in T2DM patients that may improve key outcomes including body weight, fasting glucose and postprandial variability. These findings should be viewed as exploratory, and a larger, longer study is necessary to corroborate these findings.

Key words: Intermittent fasting; Type 2 diabetes; Remote food photography; Self-monitored blood glucose; Homeostasis model of assessment for insulin resistence index

Core tip: Intermittent fasting (IF) involves limiting food intake into a single 4 to 8 h period, daily. We observed the tolerability, safety and health benefits of IF in 10 type 2 diabetes mellitus (T2DM) patients during a 2-wk IF intervention. Outcomes were measured after the three study phases; baseline, intervention, and follow-up. Although short, the IF phase significantly improved weight loss and fasting glucose levels, was well tolerated, and hypoglycemia was not observed. During follow-up, glucose levels reverted. This simple, outpatient-directed dietary manipulation may prove valuable in T2DM individuals with exercise intolerance, who are resistant to complex diet regimes, or are not at glycemic goals.

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INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) is reaching epidemic levels worldwide, and correlates with rising obesity rates and sedentary lifestyles. In fact, it is predicted that 439 million adults will have diabetes by 2030[1]. This is significant, as diabetes is closely associated with cardiovascular disease, retinopathy, neuropathy, and kidney disease. In turn, this places increasing stress on the health care system, and these patients utilize medical resources three to four times the amount of those without diabetes[2].

Modest weight loss and exercise regimes can both prevent the onset of T2DM and improve metabolic control[3]. According to most national diabetes associations and clinical practice, dietary interventions are considered essential in the treatment and prevention of diabetes-related complications[4]. There are many types of dietary interventions people may use; one of which is intermittent fasting (IF). This is a dietary intervention that time-restricts feeding to 4-6 h and extends the overnight fast from 12 towards 18 or 20 h, may be a beneficial additional dietary strategy used in T2DM management.

After diagnosis, most individuals (depending on individual circumstances) with T2DM are given management goals of an HbA1c below 7.0%, FPG 4.0-7.0 mmol/L, and post-prandial levels of 5.0-10.0 mmol/L[3,5,6]. Self-monitoring of blood glucose (SMBG) using glucometers can be critical for patient feedback and recognition of glucose control, as symptoms poorly predict glucose levels alone. Glucose goals are typically reached through an individualized treatment regime including lifestyle (diet and exercise) and medication use, yet a great number fail to reach, or maintain, these diabetic goals. As a result, a plethora of medication combinations are tried, as are weight loss approaches including consideration for bariatric surgery for morbidly obese individuals. Given the intense focus on weight and dietary measures, IF has the potential to be included in the armament in the fight to improve SMBG levels while contributing to weight loss in those in whom it would be beneficial.

In addition to glucose levels and body weight, there are other important aspects of T2DM worth considering. First is the degree of insulin resistance, which theore-

tically contributes to the difficulty of maintaining euglycemia[7]. Outside of the research clinic, insulin resistance can be measured in healthy patients using surrogate index measures derived from glucose and insulin measures in the fasting state. These surrogate index measures include glucose/insulin ratio, log fasting insulin, Homeostasis Model Assessment (HOMA-IR), log HOMA-IR, and Quantitative Insulin Sensitivity Check Index (QUICK1). A decrease in insulin resistance can improve glucose control, and exercise and weight loss both favorably decrease resistance states. Hence, we measured HOMA-IR, which has the most agreement with the clamp technique in assessing insulin resistance in T2DM patients[8], to help determine if IF may be beneficial.

Although the causal role is unknown, an association between chronic low-grade inflammation and diabetes has been shown to occur[9]. C-reactive protein (CRP) is a biomarker used to determine if inflammation is present. Elevated levels of CRP have been associated with insulin resistance, nephropathy progression and elevated fasting glucose in diabetes patients[10,11]. It is also known that CRP can be decreased with dietary therapy[12]. Hence, we measured CRP to see whether IF favorably decreased this inflammatory marker.

It can be challenging to measure dietary and exercise habits in clinical studies, and there is no defined intervention that is shown to be better than one another[13]. Monitoring devices worn daily are acceptable methods of tracking physical activity, with accelerometers being the current gold standard[14]. An alternative method to use in free-living adults is a questionnaire. Although not the gold standard, they have been shown to be a reliable method. The Yale Physical Activity Survey (YPAS) is a particular questionnaire that has shown to be reliable for capturing physical activity[14,15]. The YPAS has considerable test-retest reliability which makes it a useful tool for a repeated measures design in free living-adults[16,17]. Hence, the YPAS questionnaire was employed to track physical activity in this study.

The gold standard for measuring energy intake is the Doubly-Labelled Water method (DLW)[18]. However, this is difficult to use in those who are not experienced. One alternative to the DLW is the remote food photography method (RFPM). The RFPM has been shown to be an efficient and accurate method of capturing dietary intake in free-living adults[19,20]. Hence, the RFPM for 3 d in each of the study phases was utilized in this study to capture estimates of energy intake.

The Canadian Diabetes Association (CDA) publishes Clinical Practice Guidelines that currently recommends that individuals with T2DM follow the Canada Food Guide for nutritional needs[21]. Further, the CDA promotes various other nutritional strategies, such as portion control, carbohydrate counting, and grouping foods according to their glycemic index[4]. While these are all appropriate recommendations, some people have difficulty grasping these suggestions and fitting them into their diet[22]. Even an activity as simple as calorie-counting has been reported to lead to an increase in self-perceived psychological stress and cortisol levels, effects not seen when participants restricted calories unintentionally[23].

Another valuable resource for helping attain nutritional and diabetic goals is for patients to see a dietitian and/or attend a self-management program. However, many barriers exist for patients to access these programs or adhering to dietary advice[24]. Some of the barriers listed by people with diabetes range from feelings of helplessness and frustration, to not attaining desired glycemic control, to not being able to accommodate suggestions regarding food restrictions[22,25].

To overcome some of the barriers that some diabetes patients face with dietary interventions, alternative solutions should be explored. An example of an alternative dietary solution is IF. There are many variations of IF, but it is essentially restricting caloric intake to a specified period of time. One method of IF is to have people restrict their caloric intake for 18 to 20 h per day and eat *ad libidum* during those other 4 to 6 h. The feeding period will usually occur midday to early evening, and an increased protein intake may or may not be recommended to help increase satiety. During the fasting period, people are allowed to consume water, coffee, or tea. With this method of IF, caloric intake occurs when there is a diurnal peak in insulin sensitivity, and, similarly, a diurnal peal in cortisol levels during the fasting period. This may theoretically benefit glucose control. Similar protocols have been shown to have beneficial effects in non-diabetic populations with varying effects on glucose uptake, lipid levels, cortisol levels, and body fat[26-29]. Previous studies have shown that an IF intervention whereby all of one's daily calorie consumption are consumed in a four-hour window led to participants feeling too full and some weight loss, despite recommendations to consume more calories[26,27]. Hence, it is possible that IF can lead to a spontaneous caloric deficit in adult patients in their homes[30]. However, another study found that an IF intervention led to worsening of glycemic control[27], hence there are conflicting results as to its overall effects in a healthy individuals.

IF has received increasing attention for its potential therapeutic role in the treatment and prevention of cardiovascular disease and T2DM. However, we could only identify 2 studies in the literature evaluating the effects of IF in T2DM, although other trials are ongoing. The first evaluated a Mediterranean-style diet, with and without breakfast, on postprandial glucose, insulin, triglycerides and gastric inhibitory polypeptide in individuals with T2DM over a single day[31]. The Mediterranean lunch without breakfast revealed no increase in glucose, insulin, or triglycerides during the breakfast period (despite coffee intake), which did significantly increase above baseline during the comparator arms of low-fat and low-carbohydrate breakfasts. Another 12-wk had people undergo an IF fast whereby they only consumed caloric content in

the morning and early afternoon, and in this study, a decrease in FBG, HbA1c, and an improved response to an OGTT were observed[32]. Given these potential benefits, we designed a short-term observational pilot study to assess tolerability, safety, and specific anthropomorphic, biochemical and blood glucose health benefits of daily IF in patients with T2DM, and measured their persistence upon return to an unstructured diet.

MATERIALS AND METHODS

Recruitment

Participants were recruited from within the Saskatoon Health Region, which serves a population catchment of approximately 325000 people. Posters were delivered to general practitioners' offices in Saskatoon, as well as the 3 hospitals within the city of Saskatoon. Advertisements to the general public were placed in local newspapers and *via* internet outlets (*i.e*., Kijiji) alerting them of the study.

Individuals with a diagnosis of T2DM (confirmed by fasting glucose > 7.0 mmol, HbA1c > 6.5%, or OGTT > 11.0 mmol) and between the ages of 18-65 were eligible to enroll in this study. Certain medical conditions were excluded from enrollment, such as the presence of ischemic heart disease or heart failure, chronic inflammatory diseases, chronic infections, moderate to severe renal disease (GFR < 45), uncontrolled hypertension and hypoglycemic unawareness. Lastly, participants were excluded if they currently managed their diabetes with either insulin or glyburide due to their increased risk of hypoglycemia.

Study design

Interested participants that met inclusion criteria provided written consent and were educated on study procedures, and the risk, detection and management of hypoglycemia. The study was divided into 3 phases, baseline (run-in), intervention, and follow-up (Figure 1). During the baseline period, participants engaged in their normal dietary patterns (breakfast, lunch and dinner) for a period of 2 wk. During the intervention phase (weeks 3-4), participants were instructed to follow the IF meal timing pattern. This consisted of a fasting goal for a period of 18-20 h per day, with *ad libidum* zero-calorie coffee, tea, and water intake during fasting hours being permitted. During feeding time, participants were allowed to eat whatever they chose, but were encouraged to include at least 1/3 plate of protein to promote satiety (visual representations provided during training). The intervention phase was followed by a 2 wk follow-up phase with normal dietary patterns. There were no embedded criteria for weight loss, calorie restriction, or changes to exercise habits for the participants.

Assessment and evaluation

Self-reporting: Hours fasted, SMBG, caloric intake and exercise were all self-reported. Throughout all study phases, participants reported SMBG 3 times daily (fasting morning, random afternoon, and postprandial evening) with the use of a glucometer and logbook that was provided to them free of charge. In the same logbook, they also kept a diary of total consecutive hours fasted each day. In each of the three time periods (baseline, intervention, follow-up) participants completed a random 3-d food diary using the RFPM. During these days, participants received customized text message prompts by study staff to ensure compliance with RFPM. Participants responded to all text prompts to confirm that they had adhered to RFPM, as well as sent images of their food (before and after consumption to capture food waste). Physical activity/spontaneous energy expenditures were captured using the YPAS tool at the end of each of the study phases.

Biochemical and anthropometric measurements: Participants underwent fasted blood draws on the last day of the baseline phase, intervention phase, and follow-up phase. Fasting insulin, fasting plasma glucose (FPG) (with subsequent calculation for HOMA-IR) and CRP were measured. On each of these days, participants also underwent anthropometric measurements (height, weight, blood pressure, waist circumference). These measurements were all performed by the same individual.

Statistical analysis

All statistical procedures were performed on SPSS v. 22 and STATA v. 13. Data preparation was done using Excel 2011 and STATA v. 13. Significance was set at alpha = 0.05 (95%CI) for all tests. Repeat measures ANOVA were performed for measuring changes in anthropometric and biochemical changes.

The group means and standard deviations of days 1 through 42 (6 wk total study time) were calculated individually for three daily measurements: fasted morning (M), random afternoon (A), and postprandial evening (E) SMBG measurements. Linear and quadratic regression of group means and standard deviations were used to explore the relationship between study phase and SMBG.

OLR was used to explore the impact of relative daily fasting duration on SMBG. Cut-offs for OLR were created using standards for the diabetic fasting goal (< 7.0 mmol/L) and frank hyperglycemia (> 11.1 mmol/L), with an additional midpoint (9.05 mmol/L). The variable created for OLR was the hours fasted difference (HFD), the difference between actual hours fasted and the average hours fasted during the baseline phase (Table 1).

No category was created to represent hypoglycemic events, as none were recorded throughout the duration of the study.

RESULTS

Baseline participant characteristics

Summarized in Table 2 are the anthropomorphic and

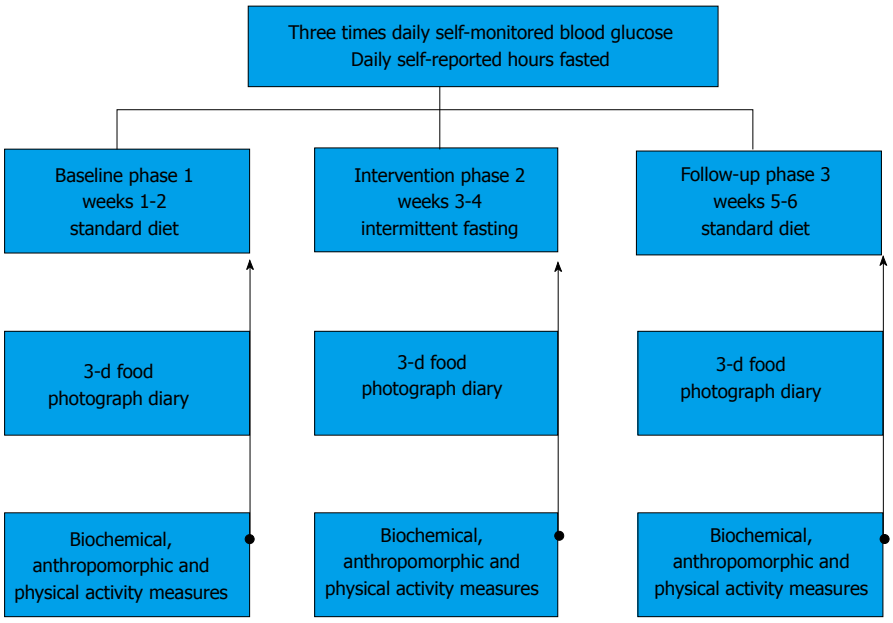

Figure 1 Study design. During the three-phase, 6 wk study, participants engaged in normal dietary patterns (breakfast, lunch and dinner) during weeks 1-2 (Phase 1, baseline) and 5-6 (Phase 3, follow-up). For weeks 3-4 (Phase 2, intervention) participants followed the IF meal timing pattern with a goal of daily fasts for 18-20 h per day, and a 4-6 h feeding period. *Ad libidum* zero-calorie intake, including coffee and tea during fasting hours, was permitted. Hours fasted and self-monitored blood glucose (fasted a.m., random afternoon pre-meal, postprandial evening) was reported daily throughout the study. On the last day (day 14, 28 and 42) of each phase, biochemical (fasting bloodwork), anthropomorphic (clinical assessment), and YPAS physical activity was collected. A 3-d consecutive photographic food diary was collected during each of the three phases. YPAS: Yale Physical Activity Survey; IF: Intermittent fasting.

Table 1 Cut-off points created to explore the impact of fasting on self-monitored blood glucose

SMBG value cut-off	Morning fasted	Evening postprandial
< 7.0 mmol/L	Normal/goal level	Normal/goal level
7.0-9.05 mmol/L	Above goal	Normal/goal level
9.05-11.1 mmol/L	Above goal	Above goal
> 11.1 mmol/L	Above goal	Above goal

SMBG: Self-monitored blood glucose.

Table 2 Baseline characteristics of participants

Measurement	Mean ± SD
Anthropomorphic	
Age (yr)	53.8 ± 9.11
Weight	100.6 ± 21.75 kg
BMI	36.9 ± 8.29 kg/m^2
Waist circumference	109.6 ± 11.1 cm
(reference < 88 female, < 102 male)	
Daily hours fasted	11.6 ± 1.9 h/d
Systolic BP (mmHg) T2DM goal < 130	130.00 ± 17.80
Diastolic BP (mmHg) T2DM goal < 80	80.50 ± 13.20
Biochemical	
C-reactive protein (mg/L)	4.31 ± 3.80
(reference < 1.0 mg/L)	
HOMA-IR calculated (normal < 2.5)	6.91 ± 3.00
Fasting glucose (normal < 7.0 mmol/L)	7.45 ± 1.52 mmol/L
Medications present during study period	
Metformin	10 (10)
Sulfonylureas	1 (10)
Other diabetic medications	1 (10)
Other non-diabetic medications	8 (10)

T2DM: Type 2 diabetes mellitus; HOMA-IR: Homeostasis Model Assessment; BMI: Body mass index; BP: Blood pressure.

biochemical measurements (with standard deviation) of the ten participants at study entry. Normal values for clinical and biochemical parameters are referenced. Subjects had a mean age of 53.8 years old (ranging 44-62) and BMI of 36.9 (range of 28-45 kg/m^2), the latter corresponding on average to Class II obesity, with very high disease risk compared to normal weight individuals. Insulin resistance was confirmed, with a mean HOMA-IR of 6.91, and baseline fasting blood glucose levels were above the goal of < 7.0 mmol/L (mean 7.45 mmol/L). A nonspecific biochemical marker of inflammation (CRP) was also elevated at baseline in this cohort. All participants took daily metformin as part of their diabetic management, eight as monotherapy. One participant was also taking gliclazide while another was also using liraglutide.

The clinical and biochemical changes resulting from a 2 wk dietary intervention of IF are shown in Table 3. The means of the measured biochemical and anthropomorphic outcomes of all subjects were calculated for each variable within the three phases of the study, with standard deviations shown: Phase 1 (baseline), Phase 2 (intervention) and Phase 3 (follow-up). Repeat measures ANOVA comparisons between study phases were done to reveal significant differences ($P < 0.05$). Clinical measures revealed that IF decreased mean body weight, BMI, blood pressure, and waist circumference as compared to baseline with significant changes only for body weight (-1.4 kg; $P = 0.009$) and BMI (-0.52; $P = 0.01$). The beneficial changes observed

Table 3 Differences between Study Phases for Biochemical and Anthropometric Parameters

Measurement	Mean ± SD Phase 1	Mean ± SD Phase 2	Mean ± SD Phase 3	Mean difference Phase 1 to 2	Mean difference Phase 2 to 3	Mean difference Phase 1 to 3
Clinical outcome						
Weight (kg)	100.6 ± 21.7	99.2 ± 21.3	99.5 ± 21.5	-1.4 (P = 0.009)	+0.28 (P = 1.0)	-1.12 (P = 0.08)
BMI (kg/m^2)	36.9 ± 8.3	36.4 ± 8.1	36.5 ± 8.1	-0.52 (P = 0.01)	+0.1 (P = 1.0)	-0.42 (P = 0.09)
Waist circumference (cm)	109.6 ± 11.1	107.8 ± 11.1	107.5 ± 10.9	-1.75 (P = 0.086)	-0.30 (P = 1.0)	-2.05 (P = 0.24)
Systolic BP (mmHg)	130.0 ± 17.8	127.0 ± 21.4	128.5 ± 14.3	-3 (P = 0.83)	+1.5 (P = 1.0)	-1.5 (P = 1.0)
Diastolic BP (mmHg)	80.5 ± 13.2	79.8 ± 15.7	81.7 ± 12.2	-0.72 (P = 1.0)	+1.9 (P = 0.76)	+1.2 (P = 1.0)
Daily hours fasted	11.6 ± 1.9	16.8 ± 1.2	11.5 ± 2.0	+5.2 (P < 0.005)	-5.3 (P < 0.005)	-0.09 (P = 1.0)
Biochemical outcome						
C-reactive protein (mg/L)	4.3 ± 3.8	4.0 ± 3.7	4.1 ± 3.5	-0.3 (P = 0.9)	+0.09 (P = 1.0)	-0.25 (P = 1.0)
HOMA-IR	6.9 ± 3.0	6.5 ± 2.4	6.6 ± 3.0	-0.46 (P = 1.0)	+0.11 (P = 1.0)	-0.35 (P = 1.0)

HOMA-IR: Homeostasis Model Assessment; BMI: Body mass index; BP: Blood pressure.

Table 4 Morning, afternoon and postprandial self-monitored blood glucose levels decreased during intermittent fasting

14 d averaged SMBG pooled	Mean ± SD Phase 1	Mean ± SD Phase 2	Mean ± SD Phase 3	% change from Phase 1 to 2	% change from Phase 2 to 3
μfasting SMBG	8.2 ± 1.3	7.7 ± 1.8	8.1 ± 1.4	-6.10%	+5.20%
μafternoon SMBG	7.5 ± 1.0	7.2 ± 1.2	7.0 ± 0.9	-4.00%	-2.80%
μpost prandial SMBG	8.7 ± 1.9	8.6 ± 1.9	8.8 ± 1.7	-1.10%	+2.30%

μ: Average; SMBG: Self-monitored blood glucose.

were not sustained once the IF was complete. After a return to normal diet (Phase 3, follow-up), there was an inflection back toward baseline values for all parameters except a further non-significant decrease in waist circumference (-0.3, P = 1.0). All participants increased their fasting time during the intervention phase. The daily hours fasting increased from a baseline of 11.6 to 16.8 h during the intervention phase (+5.2 h; P < 0.001), and essentially returned to baseline (11.5 h) after the follow-up period.

The averages of SMBG reported daily from home glucometers decreased during the intervention phase for fasting morning, afternoon and postprandial time points (Table 4). Pooled averages of SMBG taken three times daily throughout the study are presented by study phase, indicating the % change from baseline to IF (Phase 1 to 2), and IF to follow-up (Phase 2 to 3).

IF improves morning fasted glucose levels and decreases postprandial variability. To further investigate potential benefits of IF on glucose levels, daily (rather than grouped by study phase) SMBGs were plotted over the 42 d study (Figure 2A). To investigate the glucose variances from the mean for fasting morning glucose levels, the Kolmogorov-Smirnov (KS) test was used. Figure 2B indicates that the daily distribution of morning SMBG was greatest during the intervention as compared to baseline (P = 0.002), or follow-up (P = 0.003) phases. Lastly, a similar assessment of the daily variation from the mean for evening postprandial values (Figure 2C) demonstrates wide scatter throughout all phases, with decreases in glucose variability from baseline to intervention, as well as from intervention to follow-up phase. A significant difference was found for evening SMBG distributions (P = 0.044) between the intervention and follow-up phases only (all other phases P > 0.1). There were no statistically significant differences observed between any phases for the afternoon SMBG distributions (P > 0.1).

IF enhances the proportion of fasting SMBG at goal and decreases postprandial glucose excursions. Raw SMBG counts and percentages of SMBG residing within defined glucose categories were tabulated for each study phase. Table 5 reflects morning fasted and evening post-prandial SMBG. SMBG results were placed within four discrete glucose ranges including normal/target fasting (< 7 mmol/L), frank hyperglycemia (> 11.1 mmol/L), and an equal cut-off bridging the two (cut off at 9.05 mmol/L) to determine the cause of the increased variation noted for morning SMBG during IF. The distributed results for fasting SMBG readings Table 5 highlight that the incidence of at-goal SMBG < 7.0 mmol/L increased 2.5-fold during the IF intervention (13.8% baseline increased to 34.1% during IF). Also noted during IF was the overall decrease in fasting hyperglycemia (> 7.0 mmol/L) that was offset by a greater incidence of elevated fasting levels (> 11.1 mmol/L noted at 0.8% baseline, increasing to 7.1% during IF). The improvement of readings at target glucose levels was lost during follow up, upon return to normal eating patterns.

Considering the pooled incidence of evening post-prandial SMBG up to and including 9.05 mmol/L as "at-goal" for postprandial blood glucose, IF resulted in a higher proportion in the desirable range (Table 5). Specifically, 65.7% of SMBG were < 9.05 mmol/L during the IF phase of the study, compared to 52.6%

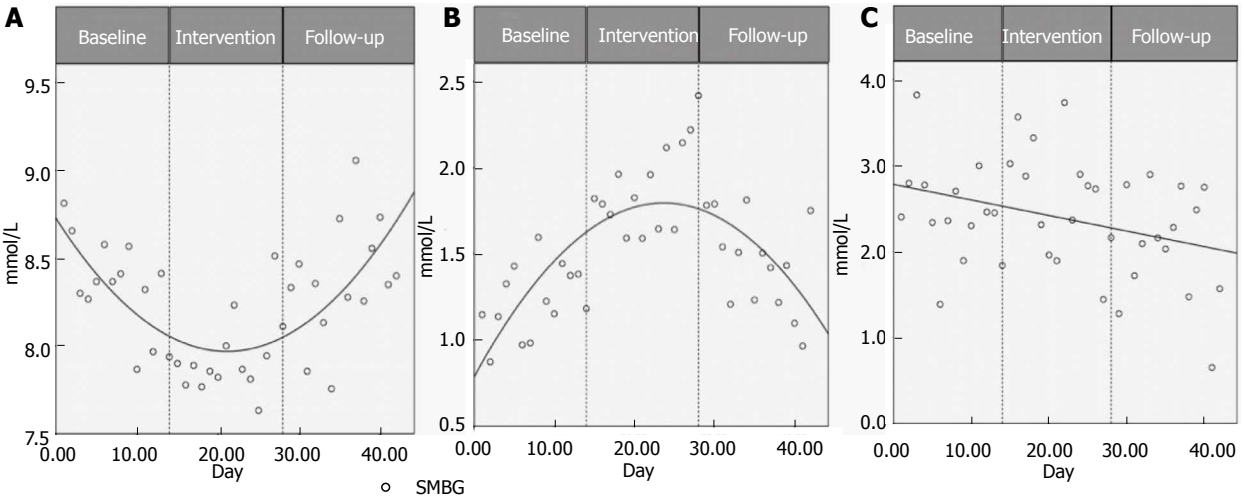

Figure 2 Intermittent Fasting improves morning fasted glucose levels and decreases postprandial variability. The daily means for fasting morning glucose levels (from personal glucometers) on days 1 through 42 are shown in Figure 2A, with the three phases indicated. Means were calculated from pooled SMBG data from the nine individuals that provided complete log sets. Figure 2B represents the daily variance from the mean for fasting morning SMBG, days 1-42, using the Kolmogorov-Smirnov (KS) test. Figure 2C shows the daily variance from the mean for evening postprandial SMBG values on days 1-42. Inflection points of quadratic equations were calculated using the formula [f 1 (y) of C + Ax + B × 2 = 0] rounded down to the nearest full integer. A: Mean morning fasted SMBG; B: Morning fasted SMBG variability; C: Evening random SMBG variability. SMBG: Self-monitored blood glucose.

Table 5 Intermittent fasting improves fasting and postprandial glucose levels

Measured SMBG (mmol/L)	Baseline	Intervention	Follow-up
Morning SMBG by phase			
< 7.0	13.8%	34.1%	15.1%
7.0-9.05	52.0%	40.7%	49.6%
9.05-11.1	33.3%	18.0%	32.8%
> 11.1	0.8%	7.1%	2.5%
Evening SMBG by phase			
< 7.0	24.5%	27.7%	12.9%
7.0-9.05	28.1%	32.9%	41.6%
9.05-11.1	27.4%	19.7%	28.7%
> 11.1	20.0%	19.7%	16.8%

SMBG: Self-monitored blood glucose.

Table 6 Ordinal Logistic Regression: Relationship between Hours Fasted Difference and morning, afternoon, and evening self-monitored blood glucose

SMBG	Overall model		
	Odds ratio	*P* value	95%CI
Morning	0.91	0.004	0.85-0.97
Afternoon	0.95	0.181	0.88-1.02
Evening	1.00	0.900	0.94-1.07

SMBG: Self-monitored blood glucose.

at baseline. Similar levels (54.1%) were found at goal during the follow-up phase, as at baseline. The proportion of SMBG > 11.1 mmol/L changed little with IF. The greatest change was found in the decrease in SMBG between 9.05-11.1 mmol/L, specific to the IF phase.

The increase from baseline, rather than the absolute number, of hours fasted improves the probability of optimal glucose control. HFD was calculated for baseline and intervention phases to explore the relationship between the increase in hours fasted from baseline and SMBG improvements. In order to determine the relationship between glucose levels and time spent fasting, OLR was performed on the non-equalized data sets from the 8 participants who had completed both their daily-hours-fasted and full SMBG logs. As presented in Figure 3, these results support the previous SMBG regression findings; mean morning SMBG readings decreased, and improvements in these readings were primarily a result of increased fasting hours from baseline. The HFD and OLR models showed a statistically significant association between change in HFD with decreased SMBG morning readings (χ^2 likelihood ratio = 8.36, P = 0.004) but not for afternoon or evening SMBG readings (P > 0.1, Table 6).

The IF phase was associated with spontaneous decreases in caloric intake and increases in physical activity. To calculate energy intake during the study, five (baseline and intervention) and four (follow-up) participants recorded their food intake *via* the RFPM. This was performed for 3 d of each study phase. From this, estimates of the total kcal/day, and the proportionate contribution from protein, carbohydrate and fat was determined as shown in Table 7. Total kcal/day decreased 18.6% with the IF intervention, and further decreased 6% into the follow-up phase. Carbohydrate and fat intake decreased 33% and 36% respectively during the IF period, whereas protein intake remained constant. To estimate physical activity during the study, all participants completed the YPAS once during each of the three phases. From this survey, an estimate of physical activity (kcal/wk) during the three study phases was determined. During the intervention phase, physical activity increased (+1856.3 kcal/wk), but then decreased at study end (in the follow-up phase; -2449.6 kcal/wk).

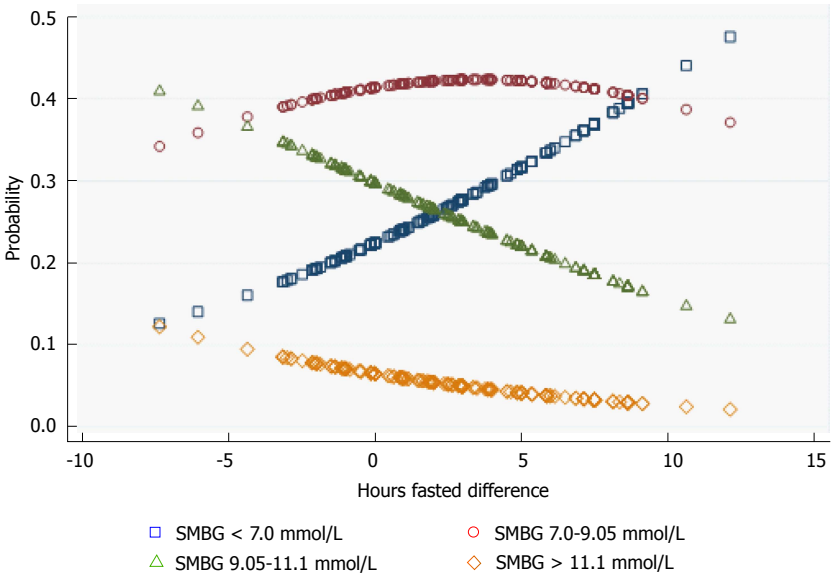

Figure 3 Positive relationship between hours fasted and morning glucose levels. Ordinal logistic regression (OLR) tested the association between the increase in hours fasted from baseline, and the morning fasting glucose levels within the four glucose ranges noted. OLR was performed using data from the 8 individuals who had completed both their full SMBG logs and daily hours fasted logs. OLR models used the non-equalized data. Hours Fasted Difference (HFD) was calculated for baseline and intervention phases only. SMBG: Self-monitored blood glucose.

Table 7 Patient reported diet composition and physical activity, by study phase

Measure	Baseline (mean ± SD)	Intervention (mean ± SD)	Follow-up (mean ± SD)
Extrapolated energy intake (kcal/d)	1904.3 ± 404.1	1605.7 ± 375.5	1510.5 ± 755.4[1]
Protein intake (g/d)	94.2 ± 26.6	93.2 ± 26.1	79.4 ± 30.7[1]
Carbohydrate intake (g/d)	190.6 ± 58.5	142.7 ± 62.1	164.2 ± 93.9[1]
Fat intake (g/d)	86.9 ± 16.6	63.6 ± 25.2	60.9 ± 35.5[1]
Physical activity (kcal/wk)	4922.3 ± 3774.4	6778.56 ± 4329.5	4329.0 ± 3440.8

[1]Data from 4 participants.

DISCUSSION

Key findings

Many individuals with T2DM would benefit from a simple and accessible nutrition intervention that is simple to implement and teach, and improves their glycemic control. Teaching diabetes patients about IF only required between 15-30 min of the study coordinator's time, hence it was easy to teach. Although short term (2 wk IF intervention), and without oversight (self-reported and self-controlled eating hours), the intervention resulted in significant improvements in diabetic glucose control. The IF phase yielded a significant increase in the incidence of fasting blood sugars at target (34.1% *vs* 13.4% baseline), and favorable decreases in postprandial hyperglycemia (39.4% *vs* 47.4% baseline). There was also a spontaneous 18% decrease in caloric intake and increase in energy expenditure (+1856 kcal/wk), coinciding with a significant decrease in weight ($P < 0.009$) and BMI ($P = 0.01$). A strong association between the increase in hours fasted from baseline, and the probability of attaining a normal fasting glucose level was found (+LR 8.36), despite few individuals reaching the 18-20 h fasting goal. We did not find statistically significant changes to blood pressure, insulin resistance or inflammatory markers after 2 wk of IF, although all trended towards normal during this phase. Importantly, the diet was found to be tolerable and safe, with zero incidences of hypoglycemia.

Upon a return to normal eating habits, the improvements to fasting glucose levels reversed to baseline, a trend also seen for the non-significant improvements in CRP, HOMA-IR and BP. The sample size of this study is too small to determine if the sustained decreases in waist circumference, postprandial glucose variability, and energy intake into the follow-up period are meaningful.

Comparison to other dietary outcomes

The most similar study to ours that we could identify in the literature evaluated IF was a 3 mo crossover study in T2DM patients[32]. These studies differed with respect to when participants were instructed to undergo the prolonged fasting period (participants in our study were allowed to self-select their fasting period, and chose late afternoon to early evening). Similar trends were observed with respect to weight loss and decreased waist circumference, whereas the study by Kahleova *et al*[32] also showed significant improvements in fasting insulin (and presumably insulin resistance), which our did not. In contrast, other studies in non-diabetic, normal-weight participants, have shown that IF resulted in increased insulin resistance, fasting glucose, and lipids, despite weight loss occurring[26,27]. These different observed effects between diabetic and non-diabetic individuals to similar dietary changes may be related to the differences in body weight and hyperglycemia

between the studies, or due to as yet unknown factors.

This work demonstrates that there is a correlation between hours fasted and improvements in fasted glucose levels, leading us to question if simply skipping breakfast (and thereby prolonging the fast) would improve T2DM control. A study by Thomas *et al*[33] tested the effects of skipping breakfast in obese women (without diabetes). They found that when regular breakfast eaters skipped breakfast, they had greater insulin and free fatty acid excursions in response to lunch as opposed to days when both breakfast and lunch were eaten[33]. In contrast, those who regularly skipped breakfast did not experience irregular responses at lunch, regardless of whether breakfast was eaten or not[33]. Clearly, extended fasting will not benefit all and has the potential to worsen measures of health if applied to patients with T2DM.

We also query if the observed benefits in this study arise from altering the normal eating rhythm, rather than inducing a net negative energy state (such as during fasting, or exercise). Although some evidence from animal studies suggest that biological clocks may be altered as a result of changes in feeding habits[34,35], evidence of the effects of feeding entrainment on glycemic excursions in humans are lacking.

Strengths and weaknesses of study

Our study involved ten individuals (9 female, one male) who present with the typical characteristics of the majority of the worlds' T2DM population; middle age, overweight, with insulin resistance and average fasting blood sugars above goal. There are several unique aspects to this study that provide useful information, not the least of which was the patient-controlled meal timing and content, all without caloric restriction. It is the first study designed with patients directly transitioning from their normal dietary habits, to an IF intervention, to a follow-up period to see if any of the effects were sustained. Also, the capturing of SMBG readings along with the actual total hours fasted allowed us to make inferences on this relationship, which has not been done before. Another strength is our use of the RFPM, which has been shown to have good validity[19,20]. Adherence with the study protocol, as reflected by SMBG and the recorded hours fasted, was high. Also, as a surrogate for tolerability of the IF intervention, 7/10 participants viewed the intervention as tolerable when asked, and 6/10 stating they would consider continuing a modified form of IF.

The greatest weakness was the lack of power from low recruitment, which was the limiting factor in determining clear effects of IF on markers of health in T2DM, or the detection of sustained effects during follow-up. An uneven distribution between females (n = 9) and males (n = 1) is also a limiting factor for generalizability. Also of importance to note was the failure to reach the goal of 18-20 h of fasting per day, as these longer fasting times may have accentuated health benefits more clearly. Ultimately, the 16.8 ± 1.2 h fasting during Phase 2 of the study is perhaps a true reflection of the feasibility of fasting times for this diet in free-living adults. Further a longer duration of the study phases would have allowed for comparative HbA1c measures to be done, a widely accepted marker of average changes to overall glucose control reflecting the previous three months. Lastly, it is possible that all of the SMBG testing that patients did may have in itself led to behavior changes that affected the overall recorded glucose levels. Any information learned from this observational pilot study can be used to inform a larger, longer, observational or interventional trial.

Future directions and developments

Our understanding of the association between feeding entrainment and diurnal rhythms is limited, and requires further study. Also, our study took blood draws from patients at specific time points, for study ease. Ideally, patients would have blood draws performed regular over a 24 h period so that fluctuations could be noted that may be due to diurnal variations, as the consumption of calories changes over the IF period. Since our participants only had blood draws performed in the morning, some biochemical changes that may have occurred during other time periods would have been missed. It would also be ideal for future studies to have a longer study period which would allow for significant weight loss to occur, and then see if any biochemical changes are sustained during an extended follow-up period. Of course, a larger sample size would allow for a more robust conclusion as to the association between SMBG and IF and would shed som light on the true effects on morning, afternoon and evening SMBG results.

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COMMENTS

Background

Intermittent fasting (IF) is an increasingly popularized dietary method amongst varying population groups. The reasons for its increasing popularity are multifactorial, but one of which is for weight loss. Although research has been performed evaluating an IF intervention in animals and healthy subjects, there is very little known about its effects, beneficial or otherwise, in those with type 2 diabetes.

Research frontiers

As the prevalence of diabetes continues to increase, new dietary measures are necessary to pursue, as one size does not fit all. It is possible that IF may be a good option for people with diabetes alongside other popularized diets such as the Mediterranean diet, the DASH diet, and the Newcastle diet. With type

2 diabetes affecting so many people worldwide, any new potential treatment options are welcome.

Innovations and breakthroughs

To our knowledge, there is only one other study examining IF in type 2 diabetes (Kahleova *et al*). The study varied in that patients were allowed to self-select their meal times and meal options. Further, the study showed that when practiced with self-selected meal times and meal options, there is a spontaneous reduction in caloric intake (whereas the study by Kahleova provided meals and all patients were assigned to a caloric deficit). Further, the participants chose to fast mostly in the mornings and leave their meals to nighttime, whereas the study by Kahleova had their participants eat only in the morning and afternoon, and fasted in the evenings). All told, there is very little literature examining IF in diabetes patients, and so all information can be seen as important and innovative in their approach to the treatment of type 2 diabetes.

Applications

Managing the dietary aspect of diabetes can be very difficult and tiresome for some people. It can often create unnecessary stress and sense of failure in those who are unable or unwilling to adhere to dietary recommendations to help control their blood glucose and body weight. IF is a potential alternative for certain people who wish to consume their caloric intake for the day in a manner which is not considered "recommended" for people with diabetes. It also may lead to some weight loss through less caloric consumption, which is often welcome for many people with type 2 diabetes.

Terminology

IF: An eating pattern that time-restricts feeding to 4-6 h and extends the overnight fast from 12 h towards 18 or 20 h.

Peer-review

The study is valuable and of interest as intermittent fasting is a hot topic regarding weight loss and related benefits including treatment of diabetes.

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SYSTEMATIC REVIEWS

KMAP-O framework for care management research of patients with type 2 diabetes

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Abstract

AIM

To review impacts of interventions involving self-management education, health coaching, and motivational interviewing for type 2 diabetes.

METHODS

A thorough review of the scientific literature on diabetes care and management was executed by a research team.

RESULTS

This article summarizes important findings in regard to the validity of developing a comprehensive behavioral system as a framework for empirical investigation. The behavioral system framework consists of patients' knowledge (K), motivation (M), attitude (A), and practice (P) as predictor variables for diabetes care outcomes (O). Care management strategies or health education programs serve as the intervention variable that directly influences K, M, A, and P and then indirectly affects the variability in patient care outcomes of patients with type 2 diabetes.

CONCLUSION

This review contributes to the understanding of the KMAP-O framework and how it can guide the care management of patients with type 2 diabetes. It will allow the tailoring of interventions to be more effective through knowledge enhancement, increased motivation, attitudinal changes, and improved preventive practice to reduce the progression of type 2 diabetes and comorbidities. Furthermore, the use of health information technology for enhancing changes in KMAP and communications is advocated in health promotion and development.

Key words: KMAP-O framework; Type 2 diabetes; Behavioral intervention strategies; Causal mechanisms

Core tip: A complex set of behavioral and cognitive variables related to diabetes care may influence adherence and self-care practice of patients with type 2 diabetes. This systematic review is guided by a behavioral system framework. Care management strategies or health education programs serve as intervention variables that may directly influence a patient's knowledge, motivation and attitude, self-care practice, and outcomes. This review summarizes key findings in regard to the validity of developing a comprehensive behavioral system as a framework for future empirical investigation.

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INTRODUCTION

More than 29 million people in the United States have diabetes[1]. Type 2 diabetes, which accounts for 90% to 95% of all cases, occurs when the body develops insulin resistance and cells no longer transport glucose using insulin. This leads to an overproduction from the pancreas, and eventually the pancreas does not produce enough insulin when blood sugar levels increase[2]. In 2012, the total estimated cost of diagnosed diabetes in the United States was $245 billion, including $176 billion in direct medical costs and $69 billion in lost productivity[3]. Diabetes is associated with higher risk of blindness, kidney failure, heart disease, stroke, and amputations[1]. Diabetes control requires a systematic effort of adherence to medical regimens and preventive practice in diet and exercise. A comprehensive framework for promoting diabetes care is proposed in this review of the empirical literature.

MATERIALS AND METHODS

This review is centered on type 2 diabetes from a behavioral system perspective and guided by the scientific literature published in social, behavioral, and medical science journals. The research team collectively conducted the review of studies published in the scientific literature. Both conceptual and empirical developments in health education and research are highlighted in the review.

RESULTS

KMAP-O framework for type 2 diabetes

Behavioral and social scientists have considered a behavioral systems approach to medical adherence studies. Their research is centered in the identification of how knowledge, attitude, and preventive practice may influence the variability in health and behavioral outcomes. However, this approach fails to articulate causal-specific links among these major contributing factors to outcome variations. Furthermore, the lack of attention to motivational factors in search for the determinants of health care outcomes has compounded the investigative problem that has hindered the full explication of the important role of motivation in the KAP studies.

The KMAP-O framework can be used to guide care management of type 2 diabetes patients. The first construct of the KMAP-O model is knowledge. Knowledge is "the acquisition, retention, and use of information or skills"[4,5]. Type 2 diabetes patients should have the knowledge to understand the condition, its progression, and necessary self-care practices[5].

The second construct in the model is motivation. Motivation is an individual's desire or willingness to behave in a certain way. A person can be described as unmotivated if he or she feels no impetus or inspiration to act, while a person who is energized or activated toward an end is characterized as motivated[6].

Following knowledge and motivation, attitude is the next construct in the KMAP-O framework. Attitude is a "psychological tendency that is expressed by evaluating a particular entity with some degree of favor or disfavor"[7]. A patient's attitude toward diabetes involves any preconceived ideas about the condition and its management, any feelings and emotions toward aspects of diabetes and diabetes care, and the aptness to behave in particular ways about diabetes and its management[5].

Practice is the fourth construct in the model. Practice is a demonstration of "the acquisition of knowledge (increased understanding of a problem/condition) and any change in attitude caused by the removal of misconceptions about the condition"[5]. The following seven key behaviors to practice in diabetes management, as identified by the American Association of Diabetes Educators, are healthy eating, physical activity, blood glucose monitoring, medication taking, problem solving related to diabetes self-care, reducing risks of acute and chronic complication, and healthy coping[8].

The last construct in the framework is outcome. Outcomes that are commonly assessed in type 2 diabetes patients are psychosocial measures such as quality of life (QoL), and physical measures such as blood pressure, body mass index (BMI), body weight, hemoglobin A1c (HbA1c) levels, and lipid levels. The causal specifications among the KMAP-O components are portrayed in Figure 1. This model suggests that health education or behavioral intervention(s) may directly affect knowledge, motivation, attitude and practice. The changes in knowledge, motivation and attitude may also directly influence practice variations

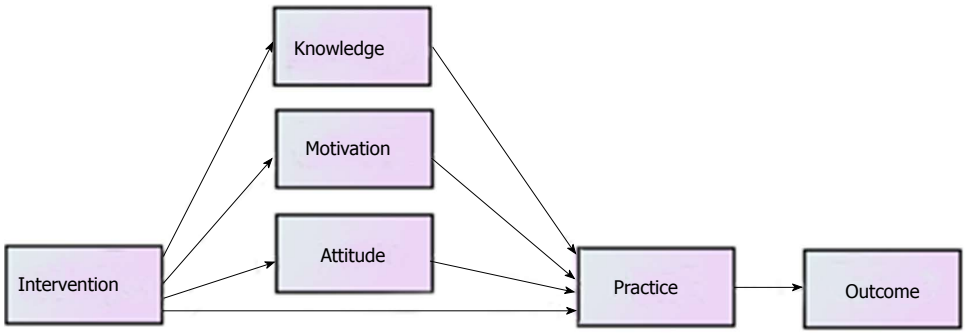

Figure 1 KMAP-O components.

in diabetes control. Consequently, better practice behavior in diabetes care management may result in a positive improvement in clinical and self-reported healthcare outcomes. These causal specifications enable researchers to generate multiple, testable hypotheses in empirical studies on care management effectiveness for type 2 diabetes.

The management of type 2 diabetes requires modification of complex behavior and practices to achieve optimal outcomes. Interventions that encourage these changes include self-management education, health coaching, and motivational interviewing. Self-management education is "a collaborative and ongoing process intended to facilitate the development of knowledge, skills, and abilities that are required for successful self-management of diabetes"[9,10]. Health coaching aims to help individuals achieve goals through the assistance of coaches that have received specific training to facilitate the change process, elicit motivation, and build trust, self-efficacy, and growth-promoting relationships. It is appropriate for type 2 diabetes management given that the coaching model is intended to address psychosocial factors and lifestyle behaviors[11]. Health coaching interventions "target health behavior changes aligned with self-determined goals leading to improved physical and mental health outcomes"[12,13]. Motivational interviewing is a patient-centered communication technique that involves open-ended questions, reflective listening, and support for patient autonomy and self-efficacy with aims to evoke intrinsic motivation of an individual to make behavior changes[14]. The objective of this review is to summarize interventions that have significantly improved knowledge, motivation, attitude, practice, and outcomes of type 2 diabetes patients.

Health education interventions

Education on knowledge, attitude, and practice: A study has reported that a health education intervention had a positive impact on the knowledge, attitude, and practice of individuals with type 2 diabetes[15].

A health education intervention consisting of 18 sessions for South Asian diabetes patients in Scotland significantly improved the low baseline scores for knowledge (+ 12.5%), serious attitudes toward diabetes (+ 13.5%), and practice (+ 20.0%)[15].

Education on knowledge, attitude, practice, and outcomes: Studies have reported that health education interventions had a positive impact on the knowledge, attitude, practice, and outcomes of individuals with type 2 diabetes[16-18].

A pharmacist-provided patient counseling in India on patients' perceptions about disease management and QoL improved knowledge, attitude, and practices scores; reduced mean capillary blood glucose levels; and improved mean scores for QoL[16].

A counseling intervention for patients during monthly sessions lasting 20-25 min for three months in South India significantly improved KAP scores, especially knowledge and attitude, and improved the outcome for postprandial blood glucose levels. However, no significant improvements in practice were reported due to high baseline scores[17].

A meta-analysis found that self-management education continually improves the outcome of HbA1c levels and suggested that knowledge and attitude continue to influence practice and outcome after the educational interventions are over[18].

Education on knowledge and outcomes: Studies have reported that health education interventions had a positive impact on the knowledge and outcomes of individuals with type 2 diabetes[19,20].

A systematic review of 72 studies evaluating the effectiveness of self-management education lasting for a period of six months or less concluded that such interventions significantly improve knowledge and glycemic control while having variable effects on lipids[19].

A community, pharmacy-based diabetes education intervention based on the American Diabetes Association standards in the United States improved knowledge of diabetes, HbA1c levels, fasting blood glucose levels, lipid levels, and blood pressure measurements[20].

Education on attitude: A study has demonstrated that a health education intervention had a positive impact on the attitude of individuals with type 2 diabetes[21].

Diabetes group education for urban, newly diagnosed patients in Ireland continually improved the patients' attitudes about the seriousness of the condition over time[21].

Education on practice and outcomes: A study has reported that a health education intervention had a positive impact on the practice and outcomes of individuals with type 2 diabetes[22].

During a health education intervention that involved access to interactive, self-paced web-based tutorials supplemented with a printout, changes in the practices of healthy eating, physical activity, blood sugar monitoring, blood pressure monitoring, foot care, and avoidance of smoking were associated with significant improvements in the outcome of HbA1c levels[22].

Education on outcomes: Studies have reported that health education interventions had a positive impact on the outcomes of individuals with type 2 diabetes[9].

A systematic review of 118 unique interventions, which involved various elements to improve participants' knowledge, skills, and ability to perform self-management activities as well as informed decision-making around goal setting, found data demonstrating that engagement in diabetes self-management education significantly decreases HbA1c levels[9].

Health coaching interventions

Coaching on attitude and outcomes: A study has reported that health coaching interventions had a positive impact on the attitude and outcomes of individuals with type 2 diabetes[11].

An integrative health coaching intervention in the United States consisting of fourteen 30-min sessions conducted over the phone, which focused on individualized visions of health and self-chosen goals, significantly decreased perceived barriers to medication adherence and improved patient activation, perceived social support, benefit finding, and HbA1c levels[11].

Coaching on practice: A study has reported that health coaching interventions had a positive impact on the practice of individuals with type 2 diabetes[23].

A three-month peer-led self-management coaching program that involved three monthly home visits and follow-up contacts through phone and email for recently diagnosed patients in the Netherlands improved the self-efficacy in intervention group patients with low baseline self-efficacy[23].

Coaching on practice and outcomes: Studies have reported that health coaching interventions had a positive impact on the practice and outcomes of individuals with type 2 diabetes[24,25].

A six-month coaching intervention in Australia consisting of monthly phone-based coaching sessions to establish and assess progress toward individualized goals for self-care activities (*e.g.*, diet, activity) and monitoring (*e.g.*, foot and eye care, vaccinations) in addition to usual care significantly improved the practices of physical activity and adherence to monitoring exams for complications, as well as the outcomes of HbA1c levels, fasting glucose, and diastolic blood pressure[24].

A 16-mo health coaching intervention at outpatient clinics in Turkey which included five or six in-person meetings and three or four telephone coaching sessions significantly improved the practice of oral health and outcome of HbA1c levels, particularly among high-risk patients, compared to formal health education[25].

Coaching on outcomes: Studies have reported that health coaching interventions had a positive impact on the outcomes of individuals with type 2 diabetes[12,26,27].

A health coaching intervention in Canada which involved weekly communication with a health coach either in-person, using a mobile device, or using a web-based wellness platform to promote goal setting and monitor progress, as well as access to a free community exercise center, improved the outcomes of HbA1c levels at three months and of body weight and waist circumference at three and six months[12].

A healthcare provider-mediated, remote coaching system *via* a PDA-type glucometer and the Internet in South Korea significantly reduced HbA1c levels (8.0% *vs* 7.5%) and total cholesterol (10.7 mmol/L *vs* 10.4 mmol/L) at three-month follow-up[26].

A clinic-based peer health coaching intervention for low-income patients with poorly controlled diabetes in the United States significantly decreased HbA1c levels to under 7.5% for 22.0% of coached mmol/L 14.9% of usual care patients at five months[27].

Motivational interviewing interventions

Motivation on knowledge and attitude: A study has reported that motivation had a positive impact on the knowledge and attitude of individuals with type 2 diabetes[28].

Training for general practitioners in motivational interviewing in Denmark significantly impacted the patients in the intervention group, who became more autonomous and motivated in their inclination to change behavior, more conscious of the importance of controlling their diabetes, and had a significantly better understanding of the ability to prevent complications[28].

Motivation on practice: Studies have reported that motivation had a positive impact on the practice of individuals with type 2 diabetes[29-31].

A 12-mo motivational interviewing-based personalized program in the United Kingdom significantly improved healthy eating habits[29].

Motivational interviewing counseling sessions for newly diagnosed patients in the Netherlands significantly improved the practice of healthy eating by reducing saturated fats[30].

A three-month motivational interviewing-based information-motivation-behavioral skills intervention for type 2 diabetes patients in the United States significantly improved the practice of healthy eating[31].

Motivation on practice and outcomes: Studies have reported that motivation had a positive impact on

the practice and outcomes of individuals with type 2 diabetes[32-37].

A 16-wk motivational interviewing intervention, in addition to a behavioral weight control program, for obese female patients in the United States significantly improved treatment adherence through higher attendance at group meetings, increased diary entries, better blood glucose monitoring, and the outcome of HbA1c levels[32].

A motivational interviewing intervention, in addition to an 18-mo weight management program, for overweight and uncontrolled female patients in the United States significantly improved treatment adherence through higher attendance at group meetings and increased diary entries, as well as the outcomes of weight loss and HbA1c levels[33].

A three-month motivational interviewing intervention in Taiwan that involved a 45- to 60-min interview, in addition to hospital-based educational sessions and the hospital's support group for diabetes patients, significantly improved patients' self-management, self-efficacy, QoL, and HbA1c levels[34].

A 13-wk motivational interviewing-based eating behavior modification program for obese patients in Thailand significantly improved the practice of healthy eating, HbA1c levels, and BMI[35].

A six-month motivational interviewing intervention with 30-min monthly sessions focusing on behavior change in an outpatient clinic after discharge for hospitalized patients with poor long-term glycemic control in China significantly improved the practice of self-management and the outcome of homeostatic model assessment for insulin resistance scores[36].

A motivational interviewing intervention for African American adults in the United States significantly increased the odds of participants adhering to recommended physical activity level (66.7% *vs* 38.8%) and significantly decreased glucose levels and BMI[37].

Motivation on outcomes: Studies have reported that motivation had a positive impact on the outcomes of individuals with type 2 diabetes[38,39].

A motivational interviewing intervention and a cognitive behavioral group training intervention each consisting of four 90-min sessions in Iran significantly lowered the mean BMI[38].

A two-year motivational interviewing-based behavior change counseling program for high-risk patients in the United States significantly improved blood pressure[39].

DISCUSSION

The empirical literature illustrates the beneficial impacts of interventions involving self-management education, health coaching, and motivational interviewing for diverse type 2 diabetes patients. This review contributes to the understanding of the KMAP-O framework and how it can guide the care management of patients with type 2 diabetes. It will allow the tailoring of interventions to be more effective through knowledge enhancement, increased motivation, attitudinal changes, and improved preventive practice to reduce the progression of type 2 diabetes and comorbidities. To ensure the effectiveness of such interventions, outcome tracking can be conducted through longitudinal observations of patients and their knowledge, motivation levels, attitude, practice, and outcomes.

Multiple clinical symptoms such as low plasma adiponectin[40], obesity and sarcopenia[41], and defective fat oxidation capacity[42] are linked with type 2 diabetes. Thus, clinical interventions should be designed carefully through causal specifications of the etiology of type 2 diabetes. Obesity is considered a leading cause for type 2 diabetes and cardiovascular disease. It is concluded that diabetes care should not only pay attention to clinical symptoms or etiologies associated with diabetes, but also consider behavioral factors that could either impede or facilitate patient adherence and self-care management of a controllable chronic condition. Furthermore, the efficacy of health promotional strategies, using the KMAP-O framework, can be demonstrated by carefully designed and executed clinical trial studies that are augmented with health information technology[43].

COMMENTS

Background

This manuscript summarized the relevance of behavioral components of health education that can improve diabetes care. Type 2 diabetes is considered an ambulatory care sensitive condition. Proper implementation of care management strategies can prevent unnecessary hospital admissions and readmissions.

Research frontiers

This manuscript introduced a comprehensive model grounded by behavioral and social science theories through a careful review of the scientific literature and document relevant strategies for implementing diabetes education and achieving diabetes control.

Innovations and breakthroughs

This manuscript articulated the potential causal mechanisms for enhancing preventive practice and improving patient care outcomes of type 2 diabetes.

Applications

This manuscript suggested plausible causal links between health educational intervention and patient care outcomes mediated by behavioral factors such as knowledge, motivation, attitude, and practice relevant to diabetes care.

Peer-review

This manuscript is a literature review on impacts of interventions involving self-management education, health coaching, and motivational interviewing for diverse type 2 diabetes patients.

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