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Contents

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Contents

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ORIGINAL ARTICLE

Complications of continuous intraperitoneal insulin infusion with an implantable pump

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Abstract

AIM: To monitor the course of continuous intraperitoneal insulin infusion (CIPII) and to gain more insight into possible complications.

METHODS: A retrospective, longitudinal observational cohort study in patients with type 1 diabetes mellitus (T1DM) was performed. Only patients with "brittle" T1DM who started CIPII between January 1, 2000 and June 1, 2011, and were treated in the only centre in The Netherlands providing CIPII treatment (Isala clinics, Zwolle) were eligible for inclusion. Outcomes were defined as operation-free period (OFP), rate and type of complications. Subanalyses were made between patients starting CIPII from 2000 to 2007 and from 2007 onwards in order to study possible changes over time in complications and/or OFP. The OFP was calculated as the time from initial implantation to the date of first documented re-operation. If patients had not experienced an operation, their data were recorded at the date of last follow up or death. Kaplan-Meier curves were constructed to visualize the OFP. A (two-sided) *P* value of less than 0.05 was considered statistically significant.

RESULTS: Fifty-seven patients were treated with CIPII, although one patient was excluded from analyses because of self-induced complications. In the remaining 56 patients, 70 complications occurred during 283 patient years. Catheter occlusion (32.9%), pump dysfunction (17.1%), pain at the pump site (15.7%) and infections (10.0%) were the most frequent complications. This resulted in a median OFP of 4.5 years (95% confidence interval 4.1-4.8 years) without any difference between the time periods. Fifty re-operations were performed because of complications, one per 5.6 patient years, with a decrease in pump dysfunction (*P* = 0.04) and pump explantations (*P* = 0.02) after 2007. In total, 9 episodes of ketoacidosis occurred during follow up and there were 69 hospital re-admissions, with a median duration of 6 d. CIPII was ceased in five patients due to recurrent infections (*n* = 2), pain (*n* = 1), inadequate glycaemic control (*n* = 1) or by own choice (*n* = 1). No CIPII related mortality was reported.

CONCLUSION: The OFP has been stable over the last decade. No CIPII related mortality was reported. A significant decrease in pump dysfunction and explantation was seen after 2007 compared to the period 2000-2007. CIPII remains a safe treatment modality for specific patient groups.

Key words: Diabetes mellitus type 1; Intraperitoneal insulin infusion; Insulin infusion systems; Complications; Surgery

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INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump has been a treatment option for patients with diabetes since the 1980s. Nowadays this treatment modality is mainly used in patients with so called "brittle diabetes", i.e., failing to reach adequate glycaemic control despite intensive insulin therapy with multiple daily injections or continuous subcutaneous insulin infusion and/or having frequent hypoglycaemic episodes, or subcutaneous insulin resistance[1,2].

Although the long term feasibility and positive metabolic benefits of CIPII are established by several clinical studies, reports on the drawbacks of CIPII are relatively scarce[3,4]. Obviously, complications interfere with treatment outcome with respect to glycaemic control, costs and, most importantly, quality of life[5,6]. Furthermore, while technical problems prevented widespread use of CIPII in the past, modifications of both the catheter attached to the pump and the insulin have reduced the incidence of insulin aggregates blocking the insulin delivery, one of the major problems in earlier years[7].

Haveman *et al*[8] underlined this development by studying the complications of CIPII in patients who started with CIPII before 2007 in our hospital (Isala Clinics, Zwolle, The Netherlands). After introduction of a new battery and a change in insulin solution in 2000, the operation-free period (OFP) was estimated to increase from 21 to 78 mo. The incidence of complications such as pump site infections and catheter related problems decreased, in accordance with other studies on CIPII[5,6]. However, ongoing monitoring is necessary to observe the course of this decrease. Furthermore, following the changes in 2000 more accurate results are required on what the OFP really is as only a limited number of patients had reached a 78 mo follow-up at the time of the previous evaluation (follow-up until 2007). Thus it is essential to extend our former study to include the period from 2007 onwards.

The aim of the current study was to describe the complications of CIPII in patients with type 1 diabetes mellitus (T1DM) over the period from 2000 until 2011. We also studies in detail the origin and consequences of both pump- and/or catheter related problems and complications.

MATERIALS AND METHODS

Patients

In the Netherlands, the following indications for CIPII have been formulated: subcutaneous insulin resistance, brittle diabetes, hypoglycaemia unawareness, delayed insulin absorption, allergies, lipohypertrophy and/or lipoatrophy, very lean subjects, needle phobia, severe skin scarring or chronic dermatological problems[9]. Patients were selected for CIPII after consultation with diabetes professionals well acquainted with CIPII with, as a minimum, the participation of an internist and a diabetes specialist nurse in the decision making. Implantation was always combined with intensive education and, when indicated, assessment by a psychologist.

All patients with T1DM who were treated with CIPII over the period from January 1, 2000 to June 1, 2011 were included in the current analysis. All of these patients were referred to and treated in the Isala Clinics in Zwolle, the only centre in The Netherlands providing this treatment. For all patients, detailed clinical data regarding surgical placement of the pump, short- and long-term complications and consequences were collected retrospectively by reviewing hospital charts, operation- and microbiology reports. Data were collected by use of standardized case record forms.

Procedures

Insulin pump, implantation and post-operative treatment and refill procedures have been described previously[8]. In Brief, MiniMed MIP model 2007 CIPII devices (Medtronic-MiniMed, Northridge, CA, United States) were implanted in our clinic from 2000 onwards. This model has a reservoir which can contains 15 mL of a special solution of U400 insulin and has a battery with 7 years longevity.

An outpatient rinse procedure with NaOH was performed every 9 mo or in cases of insulin underdelivery. Insulin underdelivery is present when, after the pump reservoir is totally emptied, the ratio between programmed and actually infused volume of programmed insulin, calculated as % error, is higher than 20%. If the % error was higher than 20, or a clinically significant difference between the % error calculated at previous refill was found, a rinse procedure was performed. In addition, inspection of the patient-pump-communicator for hardware or electronic failure was performed. If these procedures failed to restore normal insulin infusion a catheter flushing and/or catheter X-ray investigation was also performed. In case of signs of intractable occlusion despite all of these actions, surgical examination of the catheter to discover possible blockages with a post-surgical rinse of the pump was deemed necessary.

Table 1 Baseline characteristics of patients starting continuous intraperitoneal insulin infusion *n* (%)

	All patients	Implantation date	
	2000-2011 (*n* = 56)	2000-2007 (*n* = 37)	2007-2011 (*n* = 19)
Age (mean ± SD, yr)	37.6 ± 14.5	38.0 ± 14.4	36.6 ± 15.1
Female sex	38 (68)	28 (76)	10 (53)
Smokers	12 (21.4)	7 (18.9)	5 (26.3)
Previous abdominal operation	9 (16.1)	7 (18.9)	2 (10.5)
BMI (mean ± SD, kg/m^2)	25.4 ± 4.4	26.3 ± 4.2	23.7 ± 4.3
Duration of diabetes (yr), median (IQR)	16.7 (9.7-26.3)	15.9 (9.8-26.8)	19.1 (9.6-26.3)
Retinopathy	13 (23.2)	9 (24.3)	4 (21.1)
Neuropathy	17 (30.4)	12 (32.4)	5 (26.3)
Nephropathy	4 (7.1)	3 (8.0)	1 (5.3)

BMI: Body mass index; IQR: Interquartile range.

Complications

Pump-site infection was defined as a culture-proven infection in the subcutaneous pocket of the insulin pump. Prolonged device-related pain was defined as pain at the pump site which lasted for more than 6 wk after surgery and necessitated use of analgesics. Cutaneous erosion of the skin was defined as redness with signs of (imminent) perforation of the overlying skin at the pump site. Postoperative haematoma was defined as a swelling at the pump site caused by bleeding. Pump dislocation was defined as migration or rotation of the pump relative to the initial place of implantation. Catheter occlusion was defined as blockage of the catheter by fibrin clots or an intrinsic catheter defect. Encapsulation in the peritoneal cavity was defined as encapsulation of the catheter tip, positioned in the peritoneal cavity, by the omentum as diagnosed by catheter X-ray investigation or during surgical inspection. Hardware problems were defined as demonstrated hardware failure of the pump. Premature battery end-of-life was defined as battery end-of-life within 3.5 years of implantation. Pump dysfunction was defined as acute or chronic dysfunction of the pump after excluding of other causes e.g., battery end-of-life or hardware failure.

Statistical analysis

All analyses were performed using SPSS version 18.0 (Inc., Chicago, IL, United States). Descriptive statistics include number (percentage), mean ± SD and median [interquartile range (IQR)]. Data were compared with the Fisher' s exact test in the case of categorical data. In the case of continuous data, Student's *t*-test or Mann-Whitney *U* test were used if the data was distributed normally or skewed, respectively. Q-Q plots and histograms were used to determine if the tested variable had a normal distribution or not. The OFP was calculated as the time from initial implantation to the date of first documented re-operation. If patients had not experienced an operation, they data were recorded at the date of last follow up or time of death. Kaplan-Meier curves were constructed to visualize the OFP. In order to further analyze the course of the complications, subanalyses were made comparing patients starting CIPII from 2000 and 2007, the end of the previous study, and from 2007 onwards. Differences in time to the occurrence of complications and the OFP rates were assessed for statistical significance using the log-rank test. A Cox regression analysis was performed to study the influence of possible confounders (age, sex, body mass index, duration of diabetes) on the OFP. A (two-sided) *P* value of less than 0.05 was considered statistically significant.

RESULTS

Patients and implantation procedures

A total of 57 patients with T1DM were treated with CIPII. One patient with self-induced complications was excluded from analysis; the remaining 56 patients are subject of this study. Patient characteristics are depicted in Table 1. Two hundred eighty three patient years of follow up were observed, with a median duration of 4.7 years. In total, 80 pumps were implanted; 20 (35.7%) patients had a second pump and 4 (7.1%) patients had a third pump implanted.

Operation-free period

After starting CIPII, 33 patients underwent re-operation; 6 because of expected battery end-of-life, 24 because of complications and 3 for other reasons. As depicted in Figure 1, the median OFP between initial implantation and the first re-operation for all patients was 4.5 years [95% confidence interval (CI): 4.1-4.8 years]. After excluding operations for pump replacement for expected battery end-of-life or other reasons (n = 9) the median OFP was 4.5 years (95% CI: 3.9-5.0 years).

Complications

A total of 70 complications occurred during the follow-up (Table 2). Catheter occlusion (32.9%), pump dysfunction (17.1%) and pain at the pump site (15.7%) were the most frequent complications. Fifty-seven complications occurred with the first implanted pump *in situ*, 11 with the second and 2 with the third. 21 patients did not experience any complication, 15 patients experienced 1 complication, 11 patients 2 complications, 7 patients 3 complications, 1 patient 4 complications, and 1 patient 8 complications. The latter patient had recurrent infections

Table 2 Complications of continuous intraperitoneal insulin infusion during follow-up

	All patients		Implantation date			
	2000-2011 (*n* = 56)		2000-2007 (*n* = 37)		2007-2011 (*n* = 19)	
	n (%)	Per 100 PY	*n* (%)	Per 100 PY	*n* (%)	Per 100 PY
Haematoma	3 (4.3)	1.1	2 (3.8)	0.9	1 (5.9)	1.8
Infection	7 (10.0)	2.5	4 (7.5)	1.8	3 (17.6)	5.3
Pain	11 (15.7)	3.9	8 (15.1)	3.5	3 (17.6)	5.3
Cutaneous erosion	2 (2.9)	0.7	2 (3.8)	0.9	0 (0.0)	0.0
Dislocation	3 (4.3)	1.1	2 (3.8)	0.9	1 (5.9)	1.8
Hardware failure	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Premature battery end of life	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Insulin aggregate	4 (5.7)	1.4	4 (7.5)	1.8	0 (0.0)	0.0
Catheter occlusion	23 (32.9)	8.1	16 (30.2)	7.1	7 (41.2)	12.3
Encapsulation of the catheter tip	3 (4.3)	1.1	3 (5.7)	1.3	0 (0.0)	0.0
Peritonitis	1 (1.4)	0.4	1 (1.9)	0.4	0 (0.0)	0.0
Pump dysfunction	12 (17.1)	4.2	11[1] (20.8)	4.9	1[1] (5.9)	1.8
Other	1 (1.4)	0.4	0 (0.0)	0.0	1 (5.9)	1.8
All	70 (100.0)	24.8	53 (100.0)	23.5	17 (100.0)	29.9

[1]*P* = 0.04. PY: Patient years.

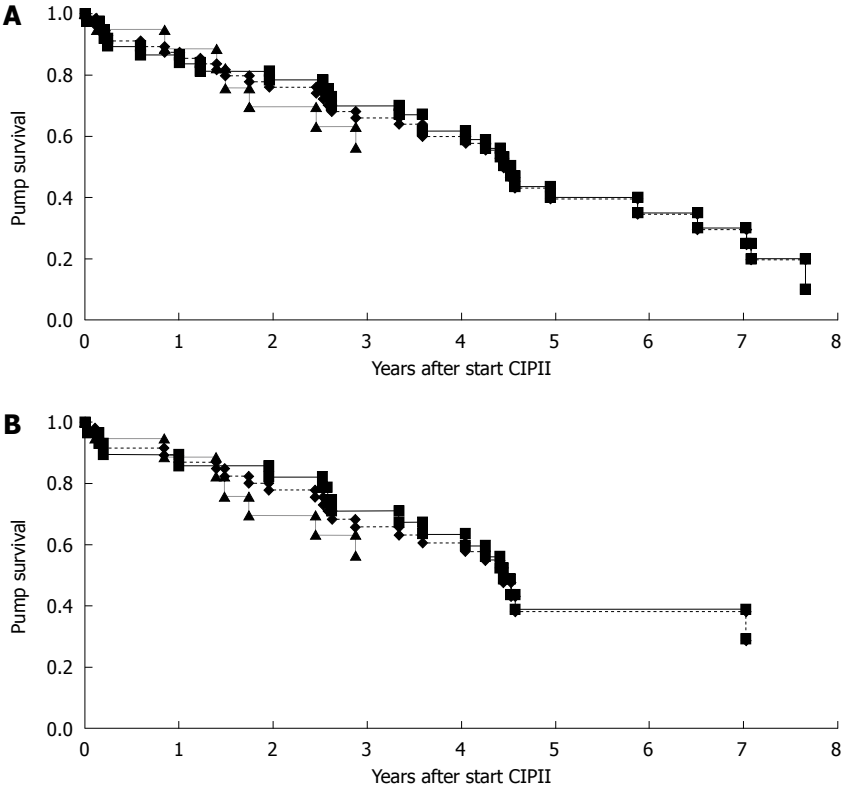

Figure 1 Time between initial implantation and first re-operation, for all reasons (*n* = 56) (A) and only for complications (*n* = 47) (B). The dotted line represents all patients. The balck line and grey line represent patients groups who started continuous intraperitoneal insulin infusion (CIPII) between 2000 and 2007 or between 2007 and 2011, respectively (log rank test for differences, A: *P* = 0.8; B: *P* = 0.72).

and peritonitis, after a catheter replacement procedure. The median time from implantation of the first pump to occurrence of the first complication (excluding battery end of life) was 3.6 years (95% CI: 2.2-5.0 years).

Consequences of complications

Because of complications, 50 re-operations were performed: one per 5.6-year of follow up (Table 3). Explantation of the pump and catheter (34.0%, 6.0 per 100 patient years) and catheter replacement (26.0%, 4.6 per 100 patient years) were the most frequently performed re-operations. Nine episodes of ketoacidosis occurred during follow up, 8 due to pump dysfunction and 1 due to catheter occlusion. Sixty-nine hospital re-admissions were caused by complications. The median duration of admission was 6 d (IQR: 3.0-12.8 d).

Table 3 Re-operations because of complications of continuous intraperitoneal insulin infusion during follow-up

	All patients		Implantation date			
	2000-2011 (n = 56)		2000-2007 (n = 37)		2007-2011 (n = 19)	
	n (%)	Per 100 PY	n (%)	Per 100 PY	n (%)	Per 100 PY
Catheter inspection	2 (4.0)	0.7	2 (5.3)	0.9	0 (0.0)	0.0
Catheter replacement	13 (26.0)	4.6	8 (21.1)	3.5	5 (41.7)	8.8
Explantation of pump and catheter	17 (34.0)	6.0	15[1] (39.5)	6.6	2[1] (16.7)	3.5
Repositioning of pump	2 (4.0)	0.7	2 (5.3)	0.9	0 (0.0)	0.0
Fixation of pump	2 (4.0)	0.7	1 (2.6)	0.4	1 (8.3)	1.8
Cutaneous problem	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
Intra-abdominal problem	1 (2.0)	0.4	1 (2.6)	0.4	0 (0.0)	0.0
Remove clot at tip of catheter/flush catheter	7 (14.0)	2.5	4 (10.5)	1.8	3 (25.0)	5.3
Haematoma	1 (2.0)	0.4	1 (2.6)	0.4	0 (0.0)	0.0
Reposition of catheter	3 (6.0)	1.1	3 (7.9)	1.3	0 (0.0)	0.0
Infection	2 (4.0)	0.7	1 (2.6)	1.2	1 (8.3)	1.8
All	50 (100.0)	17.7	38 (100.0)	44.3	12 (100.0)	21.1

[1]P = 0.02. PY: Patient years.

Course of complications

Between 2000 and 2007, 37 (median follow up 5.3 years) patients received a pump and 19 (median follow up 3.7 years) patients received a pump between 2007 and 2011. The clinical characteristics of patients in the two different timeframes were comparable. Median OFP period for patients initially implanted between 2000 and 2007 was 4.5 years (95% CI: 4.1-5.0 years). Only seven patients implanted after 2007 had a re-operation, therefore the median OFP could not be calculated. There were no significant differences in median OFP (log rank: P = 0.80) between the two timeframes, even when excluding operations for expected battery end-of-life and reasons other than complications (log rank: P = 0.72) (Figure 1A and B).

The number of pump dysfunctions among patients who started CIPII after 2007 was significantly lower than in the group of patients who started CIPII before 2007 (P = 0.04) (Table 2). As depicted in Table 3, from 2007 onwards there were significantly less re-operations for pump and catheter explantation following complications (P = 0.02). The Cox regression analysis showed a non-significant hazard ratio of 1.12 (95% CI: 0.46-2.75, P = 0.52) for patients implanted after 2007 compared to those who were implanted between 2000 and 2007. None of the confounders had a significant relation with time to first re-intervention.

Mortality and cessation of CIPII therapy

During the follow up period, one patient died due to heart failure whilst being treated with CIPII. In 5 patients, CIPII was stopped and the pump removed. In two patients the pump was removed because of recurrent infections and in the other cases because of pain (n = 1), inadequate glycaemic control (n = 1) or by own choice (n = 1). The remaining 50 patients are still being treated with CIPII.

DISCUSSION

The current study describes the incidence of complications in 56 patients treated with CIPII with an implanted insulin pump during the last decade. During 282.6 patient years of follow up, 70 complications occurred, i.e., one complication per 4.0 patient years. Catheter occlusion (32.9%), pump dysfunction (17.1%), pain (15.7%) and infections (10.0%) were the most frequent complications. A significant decrease in pump dysfunction and the need of premature explantation of the pump was seen in the period since 2007, compared to the period before 2007. There was a non-significant but potentially relevant increase in infections, catheter related complications and re-operations since 2007, although this did not affect the OFP during the last decade.

In the present study we report an OFP of 4.5 years (95% CI: 4.1-4.8 years) among patients who started CIPII between 2000 and 2007. This OFP differs from the OFP of 6.5 years (95% CI: 2.2-10.8 years) found by Haveman *et al*[8] among a subset of the same patients in the same period due to differences in follow up period. The current study had a longer follow up period for these patients and thus gives a more accurate estimate of the OFP.

The incidence of infections in the present study, 2.5 per 100 patient years, is comparable to previous studies on CIPII and other implanted devices[5,6,8,10-13]. Apparently, this rate has increased in patients operated on after 2007 to 5.3 infections per 100 patient years. However, all infections appeared in one patient. Due to combined improvements in pump technology, insulin stability and frequent rinse procedures, the previously high incidence of catheter blockage (between 7.8 and 57.3 per 100 patient years) has been substantially reduced[4,14-19]. In 2003, Gin *et al*[6] reported an incidence of 3.7 catheter obstructions needing surgical intervention, per 100 patient years. Although we found no difference in the course of treatment, compared to the limited recent literature on this topic, the incidence of catheter occlusions and re-operation for catheter replacement (14.5 respectively 8.8 per 100 patient years) since 2007 are rather high compared to the findings of Gin *et al*[6].

Besides the number of re-operations, the impact of complications is illustrated by the number of ketoacidosis occurrences (n = 9) and the hospital re-admissions (median duration of 6 d) following complications. DeVries *et al*[1] showed that initiation of CIPII diminishes the median duration hospital stay for patients with poorly regulated diabetes from 45 d in the year before implantation to 13 d in the year after implantation, the latter mostly due to implantation of the pump. As far as we know, the present study is the first to report on the number of hospital re-admissions due to complications. This number would strengthen future analysis of cost-effectiveness and health-related quality of life of CIPII.

This study has some limitations. First, since the follow up of the study performed by Haveman *et al*[8] ended at January 1, 2007 we decided to use this arbitrary point as cut-off for our subanalyses for the time course of the complications. Although this date is arbitrary and the numbers of patients are small, it can may give insight into changes in complications, positively and negatively, specific for a timeframe, that would need attention for the present care of these patients. Second, the exact cause of catheter or pump dysfunction could not always be determined and therefore the rate of factors such as insulin aggregates that may have led to pump dysfunction may be underestimated.

In conclusion, the median OFP for patients treated by CIPII with an implantable pump has been stable at 4.5 years over the last decade. Catheter occlusion (32.9%), pump dysfunction (17.1%), pain at the pump site (15.7%) and infections (10.0%) were the most frequent complications. There was a significant decrease in the number of pump dysfunctions and pump explantations and no significant alterations in the course of complications when comparing the period from 2000 until 2007 and that from 2007 onwards. However, the former group had a longer follow up period. This may mask a transition or possible future increase in complications and re-operations, thus suggesting a relatively stable OFP among patients. This will require ongoing investigation and thorough monitoring over the coming years.

Furthermore, since a new intraperitoneal insulin formulation had to be introduced in June 2011 since there are no batches of the original insulin formulation left, the findings of the present study should be taken into account when evaluating the effects associated with the use of the new insulin formulation. No CIPII related mortality was reported. CIPII remains a safe treatment modality for specific patient groups.

COMMENTS

Background

Intraperitoneal (IP) insulin infusion with an implantable insulin pump has been a treatment option for patients with diabetes since the 1980s. Nowadays this treatment is mainly used in patients who fail to reach adequate glycaemic control despite intensive insulin treatment with multiple daily injections or continuous subcutaneous insulin infusion. The aim of the current study was to monitor the course and to gain more insight into the surgical aspects and complications of continuous intraperitoneal insulin infusion (CIPII) using an implantable pump.

Research frontiers

CIPII using an implantable pump improves glycaemic regulation in selected patients, compared to subcutaneous insulin infusion. In addition, if IP delivery could be linked to a kind of permanent sensor, and with a logarithm between this sensor and pump, a closed loop system could be created in the future. However, the complications and surgical experience with CIPII are important factors in the clinical use of CIPII.

Innovations and breakthroughs

The median operation-free period (OFP) for patients treated by CIPII with an implantable pump has been stable at 4.5 years over the last decade. Catheter occlusion (32.9%), pump dysfunction (17.1%), pain at the pump site (15.7%) and infections (10.0%) were the most frequent complications. Fifty re-operations were performed due to complications, one per 5.6 patient years. No CIPII related mortality was reported. CIPII remains a safe treatment modality for specific patient groups.

Applications

Knowledge of the complications of CIPII adds to patient counseling and clinical care. Since a new intraperitoneal insulin formulation had to be introduced in June 2011 as there were no batches of the original insulin formulation left, the findings of the present study should be taken into account when evaluating the effects associated with the use of the new insulin formulation.

Terminology

Insulin delivered into the peritoneal space using an implantable pump. Insulin which is delivered into the peritoneal space is, to a large extent, absorbed directly (detectable within 1 h after administration) into the portal system, thereby mimicking the physiological route of insulin delivery from the pancreas. The time period between the initial operation and the first re-operation or, if patients have not experienced a re-operation, date of last follow up or death.

Peer review

The manuscript by van Dijk *et al* reports on the complications of CIPII in type 1 diabetes. This study is an important addition to the literature, as it enumerates the complications of CIPII with a follow-up period of up to 12 years. In addition to providing data for the entire patient group, they also perform a subanalysis comparing patients starting CIPII between 2000-2007 and those starting from 2007 onward. The current study provides longer follow-up of the patients who began CIPII in 2000 or later. This is most relevant to current care, as a pump battery with a longer life was introduced in 2000, as was a change in the insulin formulation used in the pump.

REFERENCES

1 **DeVries JH**, Eskes SA, Snoek FJ, Pouwer F, Van Ballegooie E, Spijker AJ, Kostense PJ, Seubert M, Heine RJ. Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: favourable effects on glycaemic control and hospital stay. *Diabet Med* 2002; **19**: 496-501

2 **Renard E**, Schaepelynck-Bélicar P. Implantable insulin pumps. A position statement about their clinical use. *Diabetes Metab* 2007; **33**: 158-166

3 **Logtenberg SJ**, van Ballegooie E, Israël-Bultman H, van Linde A, Bilo HJ. Glycaemic control, health status and treatment satisfaction with continuous intraperitoneal insulin infusion. *Neth J Med* 2007; **65**: 65-70

4 **Broussolle C**, Jeandidier N, Hanaire-Broutin H. French multicentre experience of implantable insulin pumps. The EVADIAC Study Group. Evaluation of Active Implants in Diabetes Society. *Lancet* 1994; **343**: 514-515

5 **Renard E**, Bouteleau S, Jacques-Apostol D, Lauton D, Gibert-Boulet F, Costalat G, Bringer J, Jaffiol C. Insulin underdelivery from implanted pumps using peritoneal route. Determinant role of insulin pump compatibility. *Diabetes Care* 1996; **19**: 812-817

6 **Gin H**, Renard E, Melki V, Boivin S, Schaepelynck-Bélicar P, Guerci B, Selam JL, Brun JM, Riveline JP, Estour B, Catargi B. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. *Diabetes Metab* 2003; **29**: 602-607

7 **Gin H**, Melki V, Guerci B, Catargi B. Clinical evaluation of a

newly designed compliant side port catheter for an insulin implantable pump: the EVADIAC experience. Evaluation dans le Diabete du Traitement par Implants Actifs. *Diabetes Care* 2001; **24**: 175
8 **Haveman JW**, Logtenberg SJ, Kleefstra N, Groenier KH, Bilo HJ, Blomme AM. Surgical aspects and complications of continuous intraperitoneal insulin infusion with an implantable pump. *Langenbecks Arch Surg* 2010; **395**: 65-71
9 Nederlandse Internisten Vereniging: Statement regarding indications for continuous intraperitoneal insulin infusion, 2007
10 **Bélicar P**, Lassmann-Vague V. Local adverse events associated with long-term treatment by implantable insulin pumps. The French EVADIAC Study Group experience. Evaluation dans le Diabète du Traitement par Implants Actifs. *Diabetes Care* 1998; **21**: 325-326
11 **Renard E**, Rostane T, Carriere C, Marchandin H, Jacques-Apostol D, Lauton D, Gibert-Boulet F, Bringer J. Implantable insulin pumps: infections most likely due to seeding from skin flora determine severe outcomes of pump-pocket seromas. *Diabetes Metab* 2001; **27**: 62-65
12 **Udelsman R**, Chen H, Loman K, Pitt HA, Saudek CD. Implanted programmable insulin pumps: one hundred fifty-three patient years of surgical experience. *Surgery* 1997; **122**: 1005-1011
13 **Darouiche RO**. Treatment of infections associated with surgical implants. *N Engl J Med* 2004; **350**: 1422-1429
14 One-year trial of a remote-controlled implantable insulin infusion system in type I diabetic patients. Point Study Group. *Lancet* 1988; **2**: 866-869
15 **Saudek CD**, Selam JL, Pitt HA, Waxman K, Rubio M, Jeandidier N, Turner D, Fischell RE, Charles MA. A preliminary trial of the programmable implantable medication system for insulin delivery. *N Engl J Med* 1989; **321**: 574-579
16 **Selam JL**, Micossi P, Dunn FL, Nathan DM. Clinical trial of programmable implantable insulin pump for type I diabetes. *Diabetes Care* 1992; **15**: 877-885
17 **Hanaire-Broutin H**, Broussolle C, Jeandidier N, Renard E, Guerci B, Haardt MJ, Lassmann-Vague V. Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM. A multicenter study. The EVADIAC Study Group. Evaluation dans le Diabète du Traitement par Implants Actifs. *Diabetes Care* 1995; **18**: 388-392
18 **Scavini M**, Galli L, Reich S, Eaton RP, Charles MA, Dunn FL. Catheter survival during long-term insulin therapy with an implanted programmable pump. The Implantable Insulin Pump Trial Study Group. *Diabetes Care* 1997; **20**: 610-613
19 **Renard E**, Baldet P, Picot MC, Jacques-Apostol D, Lauton D, Costalat G, Bringer J, Jaffiol C. Catheter complications associated with implantable systems for peritoneal insulin delivery. An analysis of frequency, predisposing factors, and obstructing materials. *Diabetes Care* 1995; **18**: 300-306

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ORIGINAL ARTICLE

HLA-DQB1* alleles and genetic susceptibility to type 1 diabetes mellitus

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Abstract

AIM: To determine human leukocyte antigen (HLA)-DQB1 allele association with susceptibility to type 1 diabetes (T1D) and to clinical and laboratory findings.

METHODS: This study was conducted on 85 unrelated Egyptian children with T1D recruited consecutively from the Pediatric Diabetes Endocrinology outpatients Clinic; Mansoura University Children's Hospital, Egypt. Patient mean follow up period was 2.5 years. Patients were subdivided according to level of HbA1c (optimal/suboptimal control < 8.5% and poor control ⩾ 8.5%). The control group consisted of 113 unrelated age- and sex-matched healthy subjects without T1D or other autoimmune diseases. Genomic DNA extraction was done for all subjects using a DNA isolation kit. HLA-Class Ⅱ-DQB1 allele typing was carried out with a polymerase chain reaction-sequence-specific oligonucleotide probe using a INNO-LiPA HLA-DQB1 update kit.

RESULTS: Significant differences were detected between Egyptian patients with T1D and control groups in the frequencies of DQB1*02 [44.4% *vs* 18.6%, corrected *P* value (*Pc*) < 0.001] and DQB1*03 (41.2% *vs* 24.4%, *Pc* < 0.001). Significant differences were also observed between control groups and T1D patients in the frequencies of DQB1*05 (14.6% *vs* 7.2%, *P* = 0.029) and DQB1*06 (34.1% *vs* 7.2%, *P* < 0.001). However, after correction for multiple comparisons, the significance was retained for HLA-DQB1*06 (Pc < 0.001) but lost for HLA-DQB1*05. HLA-DQB1*0201, *0202, *030201 were positively associated with T1D (*Pc* = 0.014, *Pc* < 0.001, and *Pc* < 0.001 respectively), while HLA-DQB1*060101 was negatively associated (*Pc* < 0.001) with the condition. Although the HLA-DQB1 alleles 030101 and 050101 were significantly higher in controls (*P* = 0.016, *P* = 0.025 respectively), both of them lost statistical significance after correction of *P* value. The frequency of the HLA-DQB1 genotypes 02/02, 02/03, and 03/03 was higher in T1D patients, and the frequency of the genotypes 03/06, 05/06, and 06/06 was higher in controls, these differences being statistically significant before correction. After correction, the genotypes 02/02, 02/03 in T1D, and the genotypes 03/06, 06/06 in controls were still significant (*Pc* = 0.01, *Pc* < 0.001, *Pc* < 0.001, and *Pc* = 0.04, respectively). Non-significant associations were found between the frequency HLA-DQB1 alleles and genotypes in T1D in relation to the grade of diabetic control, Microalbuminuria, age, gender, age of presentation, weight, height, frequency of diabetic ketoacidosis (*P* =

0.42), serum cholesterol, and fasting and post-prandial level of C-peptide (P = 0.83, P = 0.9, respectively).

CONCLUSION: The Current work suggests that HLA-DQB1 alleles *030201, *0202, *0201, and genotypes 02/03, 02/02 may be susceptibility risk factors for development of T1D in Egyptian children, while the HLA-DQB1*060101 allele, and 03/06, 06/06 genotypes may be protective factors. HLA-DQB1 alleles and genotypes do not contribute to microalbuminuria or grade of diabetic control.

Key words: HLA-DQB1; Type 1 diabetes; Egyptian; Genetic susceptibility; Children, Complication

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INTRODUCTION

Type 1 diabetes (T1D) mellitus is an organ-specific autoimmune disease characterized by T-cell-mediated destruction of pancreatic islets[1,2]. Both genetic and environmental factors are involved in the pathogenesis of the autoimmune process leading to the onset of this disease[3-6].

Both genome screens and studies searching candidate genes have confirmed that T1D is a heterogeneous polygenic disorder, with about 20 loci contributing to the susceptibility to disease[7-9]. It is believed that the most important genes, responsible for more than of 50% genetic risk of developing diabetes, are located in human leukocyte antigen (HLA) region on chromosome 6[10].

Although HLA class I may significantly influence the overall risk for diabetes[10], the HLA class Ⅱ loci DQA1, DQB1, and DRB1 contribute most to the genetic predisposition to T1D[11-14]. Their analysis remains the cornerstone of genetic risk stratification in the framework of diabetes prevention studies in risk groups such as family members of patients[15] or in the general population[16].

Furthermore, the existence of regional differences in the prevalence and nature of diabetes-related HLA haplo- and genotypes as a function of the incidence of the disease within Europe and other regions[17-20], necessitates the collection of HLA genotype data in the perspective of prediction and prevention studies at the regional or national level[21].

The most relevant non-HLA genes identified as susceptible for T1D are those connected with the T-cell-mediated immune response. The activity level of T-cells and their effector functions are determined by intracellular signaling pathways and related genes. These include PTPN22 and CTLA-4, both of which prevent spontaneous activation of auto-reactive cells and development of autoimmunity[22,23]. In Egyptian children, the CTLA-4 +49 GG homozygous genotype is especially associated with T1D in younger patients and with younger age of onset, while the AG heterozygote genotype is associated with moderate or poor control of T1D[24].

This study set out to determine HLA-DQB1 allele association with susceptibility and/or protection to T1D and with clinical and laboratory findings in a cohort of Egyptian children.

MATERIALS AND METHODS

Patients and healthy controls

T1D mellitus is an organ-specific autoimmune disease characterized by T-cell-mediated destruction of pancreatic islets[1,2]. This study was conducted on 85 unrelated Egyptian children with T1D recruited consecutively from the Pediatric Diabetes Endocrinology outpatients Clinic; Mansoura University Children's Hospital, Egypt. Studied patients were 35 males and 50 females. Patient mean age range was 12.52 ± 2.98 years (range 3.5-16 years) with mean age of presentation 8.5 ± 3.1 years. Patient mean follow up period was 2.5 years (range 1-6 years). Patients were subdivided according to level of HbA1c (optimal/suboptimal control < 8.5% and poor control ≥ 8.5%)[25,26].

All patients were treated by basal-bolus insulin regimen (3 rapid acting human insulin does as a bolus dose before the main meals and one intermediate acting human insulin does at bed time). Serum cholesterol measurement was carried out for all patients after overnight fast for 8-12 h. Patients were diagnosed with microalbuminuria if two of three consecutive urine samples showed elevated albumin excretion[27].

The control group consisted of 113 unrelated age- and sex-matched healthy subjects without TID or other autoimmune diseases such as autoimmune thyroid disease, living in the same geographical area and with the same ethnic origin as patients. Written informed consent was obtained from the parents of patients and controls after approval of the study protocol by the local ethical committee.

HLA class Ⅱ-DQB1 allele typing

Genomic DNA extraction was done for all samples using a DNA isolation kit (QIAmp DNA blood mini kit Cat. 51104, Qaigene, Gmbh). HLA-Class Ⅱ-DQB1 allele typing was done carried out with a polymerase chain reaction-sequence-specific oligonucleotide probe using a INNO-LiPA HLA-DQB1 update kit (Lot number 152003, Innogenetics, Belgium). Test conditions were according to manufacturer's instruction.

Statistical analysis

To compare the frequency of HLA-DQB1 alleles in children with T1D and controls, the conventional χ^2 test with Yates' correction for continuity, when appropriate, was used. SPSS version 17 was used for statistical analysis. The odds ratio (OR) was calculated with 2 × 2 contingency tables. The 95% confidence intervals were obtained using Cornfield's approximation. Data was analyzed by one-way ANOVA for multiple comparisons. The *P* value was corrected (*Pc*) for the number of alleles tested. The level of significance was set at 95%. *P* value less than 0.05 was considered significant.

RESULTS

The average weight and height of studied patients were 44.55 ± 14.51 kg and 144.6 ± 15.55 cm respectively. Microalbuminuria was found in only 5 patients. The average serum cholesterol level was 163.95 ± 28.1, and the HbA1c average level was 7.98 ± 1.59. Optimal/suboptimal control of HbA1c level was found in 57 patients, and poor control in 28 patients (Table 1).

Significant differences were detected between Egyptian patients with T1D and control groups in the frequencies of DQB1*02 (44.4% *vs* 18.6%, *Pc* < 0.001, OR: 3.5) and DQB1*03 (41.2% *vs* 24.4%, *Pc* < 0.001, OR: 2.17). Significant differences were also observed between control groups and T1D patients in the frequencies of DQB1*05 (14.6% *vs* 7.2%, *P* = 0.029, OR: 0.45) and DQB1*06 (34.1% *vs* 7.2%, *P* < 0.001, OR: 0.15). However, after correction for multiple comparisons, the significance was retained for HLA-DQB1*06 (*Pc* < 0.001) but lost for HLA-DQB1*05.

From analysis of the frequency of allele subtypes in T1D patients and controls, HLA-DQB1*0201, *0202, *030201 were found to be positively associated with T1D (*Pc* = 0.014, *Pc* < 0.001, and *Pc* < 0.001 respectively), while HLA-DQB1*060101 was negatively associated (*Pc* < 0.001). Although the HLA-DQB1 alleles 030101 and 050101 were significantly higher in controls (*P* = 0.016, *P* = 0.025 respectively), both of them lost statistical significance after correction of *P* value (Table 2).

From analysis of HLA-DQB1 genotypes in T1D patients and controls, the frequency of the genotypes 02/02, 02/03, and 03/03 was found to be higher in T1D patients, and the frequency of the genotypes 03/06, 05/06, and 06/06 was higher in controls, with these differences being statistically significant before correction. After correction, the genotypes 02/02, 02/03 in T1D, and the genotypes 03/06, 06/06 in controls still showed significant differences (*Pc* = 0.01, *Pc* < 0.001, *Pc* < 0.001, and *Pc* = 0.04, respectively) (Table 3).

In the analysis of the frequency HLA-DQB1 alleles and genotypes in T1D in relation to grade of diabetic control (Table 4), Microalbuminuria, age, gender, age of presentation, weight, height, frequency of diabetic ketoacidosis (*P* = 0.42), serum cholesterol, and level of fasting and post-prandial C-peptide (*P* = 0.83, *P* = 0.9, respectively), only non-significant associations were found (data not shown).

Table 1 Clinical and laboratory characteristics of type 1 diabetes mellitus patients

Characteristic	*n* (%)
Age (mean ± SD, yr)	12.52 ± 2.99
Age of presentation (mean ± SD, yr)	8.5 ± 3.1
Gender: mean/female	35 (41.2)/50 (58.8)
Weight (kg)	44.55 ± 14.51
Height (cm)	144.6 ± 15.55
Microalbuminuria	
No	80 (94.1)
Yes	5 (5.9)
Frequency of DKA	1.22 ± 0.91
C-peptide (fasting)	0.34 ± 0.28
C-peptide (post-prandial)	0.58 ± 0.64
Serum cholesterol	163.95 ± 28.1
HbA1c	7.98 ± 1.59
Grades of HbA1c control[1]	
Optimal/suboptimal	57 (67.1)
Poor	28 (32.9)

[1]Optimal/suboptimal control < 8.5, poor control ⩾ 8.5. DKA: Diabetic ketoacidosis.

DISCUSSION

T1D mellitus is a chronic disease which most frequently presents in childhood[28,29]. It is classified into type 1B (idiopathic) and 1A diabetes mellitus, mediated through the immune system[30,31]. In T1D 1A, a genetically susceptible individual presents with loss of tolerance to the pancreatic islet tissue triggered by environmental factors[32] and develops a progressive, immune-mediated destruction of pancreatic islet β cell[31,33].

T1D is considered a multifactorial condition with complex interactions between genetic and environmental factors[29,31]. There is evidence showing that 40%-50% of the inherited susceptibility to the disease is contributed by HLA-DR-DQ[30]. The association of specific HLA-DQB1 alleles and genotypes with T1D susceptibility/protection depends on the ethnicity and racial background of each population. For example, in Caucasians T1D is positively associated with DQB1*0201 and DQB1*0302, while in Japanese it is associated with DQB1*0401 and DQB1*0303.

From the results of the current study, significant positive associations were found with HLA-DQB1*02 and DQB1*03 (*Pc* < 0.001, OR = 3.5, OR = 2.17 respectively) and a negative association with DQB1*06 (*P* < 0.001, OR: 0.15) in Egyptian children with T1D. At the same time, HLA-DQB1*0201, *0202, *030201 were positively associated (*Pc* = 0.014, *Pc* < 0.001, and *Pc* < 0.001 respectively), and HLA-DQB1*060101 was negatively associated (*Pc* < 0.001) with T1D. The strongest positive association was found for HLA-DQB1*030201, followed by *0202, and finally *0201 (OR = 19.2, OR = 14.4, and OR = 2.21, respectively). To the best of our knowledge, the present study is the first to identify a positive association between

Table 2 HLA-DQB1 allele frequency in type-1 diabetes mellitus group *vs* control group *n* (%)

HLA-DQB1 allele	Patient (*n* = 85)	Control (*n* = 113)	OR	95% CI	*P* value	*Pc* value
02	68 (44.4)	38 (18.6)	3.5	2.19-5.65	< 0.001	< 0.001
0201	49 (32.0)	36 (17.6)	2.21	1.35-3.62	0.001	0.014
0202	19 (12.4)	2 (1.0)	14.4	3.3-62.8	< 0.001	< 0.001
03	63 (41.2)	50 (24.4)	2.17	1.38-3.41	< 0.001	< 0.001
030101	4 (2.6)	18 (8.8)	0.279	0.09-0.84	0.016	NS
030201	56 (36.6)	6 (2.9)	19.2	7.9-45.9	< 0.001	< 0.001
04	0	17 (8.3)	-	-	-	
05	11 (7.2)	30 (14.6)	0.45	0.22-0.93	0.029	NS
050101	6 (3.9)	21 (10.2)	0.35	0.14-0.91	0.025	NS
050201	6 (3.3)	1 (0.5)	6.9	0.79-59.6	0.043	NS
06	11 (7.2)	70 (34.1)	0.15	0.07-0.29	< 0.001	< 0.001
060101	2 (1.3)	51 (24.9)	0.04	0.01-0.17	< 0.001	< 0.001
0603	4 (2.6)	-	2.37	2.1-2.7	0.020	NS
060401	4 (2.6)	1 (0.5)	5.48	0.6-49.5	0.090	NS

HLA: Human leukocyte antigen; OR: Odds ratio; NS: Not significant; *Pc* value: *P* value corrected for 14 comparisons. Significant *P* value if ≤ 0.05.

Table 3 HLA-DQB1 genotype[1] frequency in type 1 diabetes mellitus group *vs* control *n* (%)

HLA-DQB1 genotype	Patient (*n* = 85)	Control (*n* = 113)	OR	95% CI	*P* value	*Pc* value
02/02	14 (16.5)	3 (2.7)	7.23	2.01-26.1	0.001	0.01
02/03	38 (44.7)	8 (7.1)	10.61	4.56-24.5	< 0.001	< 0.001
02/04	-	7 (6.3)	1.01	1.02-1.18	0.01	NS
02/05	6 (7.1)	4 (3.5)	2.07	0.56-7.57	0.26	NS
02/06	6 (7.1)	16 (14.2)	0.46	0.17-1.23	0.16	NS
03/03	12 (14.1)	6 (5.3)	2.93	1.05-8.16	0.033	NS
03/05	4 (4.7)	8 (7.1)	0.65	0.19-2.23	0.48	NS
03/06	2 (2.4)	22 (19.5)	0.1	0.02-0.44	< 0.00	< 0.001
05/06	1 (1.2)	11 (9.7)	0.11	0.01-0.87	0.012	NS
06/06	2 (2.4)	16 (14.2)	0.15	0.03-0.65	0.004	0.04

[1]Genotypes with frequency more than 5%. HLA: Human leukocyte antigen; OR: Odds ratio; NS: Not significant; *Pc* value: *P* value corrected for 10 comparisons. Significant *P* value if ≤ 0.05.

Table 4 HLA-DQB1 genotype[1] frequency in relation to grades of diabetic control *n* (%)

HLA-DQB1 genotype	Optimal control (*n* = 57)	Poor control (*n* = 28)	OR (95% CI)	*P* value
02/02	10 (65.9)	4 (60.5)	1.277 (0.36-4.49)	0.703
02/03	26 (34.1)	12 (39.5)	1.19 (0.45-2.78)	0.810
02/05	4 (39.4)	2 (28.9)	0.981 (0.18-5.71)	0.983
02/06	5 (53.0)	1 (63.2)	2.59 (0.29-23.35)	0.379
03/03	7 (7.6)	5 (7.9)	0.644 (0.19-2.25)	0.488
03/05	3	1	1.5 (0.15-15.11)	0.729
06/06	1	1	0.482 (0.03-8.01)	0.603

[1]Genotypes with frequency more than 5%. HLA: Human leukocyte antigen; OR: Odds ratio. Significant *P* value if ≤ 0.05, Optimal/suboptimal control < 8.5, poor control ≥ 8.5.

HLA-DQB1*0202 and T1D (Table 2).

DQB1*0201 and DQB1*0302 were positively associated with T1D in various ethnic populations including Asians[34,35], European[36-43], and Americans[44-46]. Similar results were reported for Arab patients from Saudi Arabia[47,48], Kuwait[49], Tunisia[50], Lebanon[51], and Israeli[52]. On the other hand, DQB1*0301 and DQB1*0601 were negatively associated with T1D in Korean[34], Latin American[46], Lebanese[51], Tunisian[50], Saudi children[47,48], Turkey[43], and Romanian[37] populations.

In the literature, there is only one previous study investigating the association of HLA-DQB1 alleles with T1D in Egyptians. Gaber *et al*[53] reported that HLA-DQB1*0201/*0302 were risk factors and *0601/*0603 were protective alleles. The two studies agree in relation to *0201, *0302, and *0601, but differ regarding *0603 in Gaber *et al*[53], and *0202 in the present work. HLA-DQB1*0603 was not detected in the controls of the present work. However, the present work was done on a different number of samples (85 patients *vs* 50 patients and 113 controls *vs* 50 controls) and a different geographical area (Delta region *vs* Cairo) from Gaber *et al*[53].

Egyptian are known to be of mixed ethnic origin (Middle Eastern, African and European)[54], so Egyptian studies are expected to add to the data available for different ethnic background[55]. To the best of our knowledge, the present study is the first one to mention the positive association between HLA-DQB1*0202 and T1D (Table 2).

These same HLA-DQ molecules are associated with diabetes risk in various Caucasian and black populations although their relative frequency in background populations varies. This is also reflected in genotypes found among T1D patients and comparison of high risk genotype frequencies is most relevant to disease susceptibility[56]. In Egyptian children with T1D, the genotypes 02/02, 02/03 were positively associated and the genotypes 03/06, 06/06 were negatively associated with the disease ($Pc = 0.01$, $Pc < 0.001$, $Pc < 0.001$, and $Pc = 0.04$, respectively) with the highest risk being with the heterozygote DQB1*02/*03 genotype (OR = 10.6) (Table 3). Similar findings were reported in the United States[44], Hungary[38], Romania[37], and Saudi Arabia[47,48].

The inheritance of HLA genes associated with T1DM would involve the presentation of diabetic autoantigen to autoreactive T-cells, thereby launching a T-cell activation cascade and the subsequent destruction of pancreatic β islet cells[57]. It is tempting, therefore, to speculate that the DQB1*0201, DQB1*0302 genotypes and the homozygote DQB1*0201 genotype predispose to the stimulation of auto-reactive T-cells, thereby precipitating β-cell-directed immunity. Individuals carrying DQB1*0301, DQB1*0602 or DQB1*0602 may have a reduced affinity for diabetic autoantigen peptides, thereby explaining the dominant, protective nature of these peptides[58].

Geo-epidemiological studies have highlighted that there is considerable geographic and ethnic variability not only in the incidence of T1D and its genetic determinants, but also in the acute and long-term complications and the resulting mortality risk associated with the disease. Comparisons of the genetic determinants of T1D in various populations have provided some evidence that the worldwide variation in incidence is at least partially determined by differences in genetic risk factors[32]. Our results showed no correlation between HLA-DQB1 and diabetic nephropathy as the number of patients with microalbuminuria was considered as a limiting factor. Rønningen *et al*[59] also found no association between HLA class Ⅱ alleles and microalbuminuria. No significant association was found between HLA-DQB1 and the degree of diabetic control. Further investigation of this issue in a large groups of diabetic patients of matched age, sex, diet and lifestyle is needed.

The Current work suggests that HLA-DQB1 alleles *030201, *0202, *0201, and genotypes 02/03, 02/02 may be a susceptibility risk factors for development of T1D in Egyptian children, and HLA-DQB1*060101 allele, 03/06, 06/06 genotypes may be protective factors. HLA-DQB1 alleles and genotypes do not contribute to the grade of diabetic control.

COMMENTS

Background

The existence of regional differences in the prevalence and nature of diabetes-related human leukocyte antigen (HLA) haplo- and genotypes as a function of the incidence of the disease within Europe and other regions, necessitates the collection of HLA genotype data from the perspective of prediction and prevention studies at the regional or national level.

Research frontiers

A significant positive associations were found with HLA-DQB1*02 and DQB1*03 and a negative association with DQB1*06. HLA-DQB1*0201, *0202, *030201 were positively associated, and HLA-DQB1*060101 was negatively associated with type 1 diabetes (T1D).

Innovations and breakthroughs

The strongest positive association was found for HLA-DQB1*030201, followed by *0202, and finally *0201. The present study may be the first to mention the positive association between HLA-DQB1*0202 and T1D.

Applications

No significant association was found between HLA-DQB1 and the degree of diabetic control. Further investigation of this issue in a large groups of diabetic patients of matched age, sex, diet and lifestyle is needed.

Peer review

The authors examined HLA-DQB1 allele association with susceptibility to T1D in a cohort of Egyptian children. They concluded that HLA-DQB1 alleles *030201, *0202, *0201, and genotypes 02/03, 02/02 may be susceptibility risk factors for development of T1D, and HLA-DQB1*060101 allele, 03/06, 06/06 genotypes may be protective factors. HLA-DQB1 alleles and genotypes do not contribute to the grade of diabetic control.

REFERENCES

1 **Anjos S**, Polychronakos C. Mechanisms of genetic susceptibility to type I diabetes: beyond HLA. *Mol Genet Metab* 2004; **81**: 187-195
2 **Pugliese A**, Eisenbarth GS. Type 1 diabetes mellitus of man: genetic susceptibility and resistance. *Adv Exp Med Biol* 2004; **552**: 170-203
3 **Bach JF**. Infections and autoimmune diseases. *J Autoimmun* 2005; **25** Suppl: 74-80
4 **Gale EA**. The rise of childhood type 1 diabetes in the 20th century. *Diabetes* 2002; **51**: 3353-3361
5 **Hyöty H**. Enterovirus infections and type 1 diabetes. *Ann Med* 2002; **34**: 138-147
6 **Myers MA**, Hettiarachchi KD, Ludeman JP, Wilson AJ, Wilson CR, Zimmet PZ. Dietary microbial toxins and type 1 diabetes. *Ann N Y Acad Sci* 2003; **1005**: 418-422
7 **Risch N**. Assessing the role of HLA-linked and unlinked determinants of disease. *Am J Hum Genet* 1987; **40**: 1-14
8 **Field LL**. Genetic linkage and association studies of Type I diabetes: challenges and rewards. *Diabetologia* 2002; **45**: 21-35
9 **Davies JL**, Kawaguchi Y, Bennett ST, Copeman JB, Cordell HJ, Pritchard LE, Reed PW, Gough SC, Jenkins SC, Palmer SM. A genome-wide search for human type 1 diabetes susceptibility genes. *Nature* 1994; **371**: 130-136
10 **Demaine AG**, Hibberd ML, Mangles D, Millward BA. A new marker in the HLA class I region is associated with the age at onset of IDDM. *Diabetologia* 1995; **38**: 623-628
11 **Khalil I**, d'Auriol L, Gobet M, Morin L, Lepage V, Deschamps I, Park MS, Degos L, Galibert F, Hors J. A combination of HLA-DQ beta Asp57-negative and HLA DQ alpha Arg52 confers susceptibility to insulin-dependent diabetes mellitus. *J Clin Invest* 1990; **85**: 1315-1319
12 **She JX**. Susceptibility to type I diabetes: HLA-DQ and DR revisited. *Immunol Today* 1996; **17**: 323-329
13 **Todd JA**, Acha-Orbea H, Bell JI, Chao N, Fronek Z, Jacob CO, McDermott M, Sinha AA, Timmerman L, Steinman L. A molecular basis for MHC class II--associated autoimmunity. *Science* 1988; **240**: 1003-1009

14 **Van der Auwera B**, Van Waeyenberge C, Schuit F, Heimberg H, Vandewalle C, Gorus F, Flament J. DRB1*0403 protects against IDDM in Caucasians with the high-risk heterozygous DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 genotype. Belgian Diabetes Registry. *Diabetes* 1995; **44**: 527-530
15 **Bingley PJ**, Bonifacio E, Gale EA. Can we really predict IDDM? *Diabetes* 1993; **42**: 213-220
16 **Gale EA**, Bingley PJ. Can we prevent IDDM? *Diabetes Care* 1994; **17**: 339-344
17 **Green A**, Gale EA, Patterson CC. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. *Lancet* 1992; **339**: 905-909
18 **Cucca F**, Muntoni F, Lampis R, Frau F, Argiolas L, Silvetti M, Angius E, Cao A, De Virgiliis S, Congia M. Combinations of specific DRB1, DQA1, DQB1 haplotypes are associated with insulin-dependent diabetes mellitus in Sardinia. *Hum Immunol* 1993; **37**: 85-94
19 **Rnningen KS**, Spurkland A, Tait BD, Drummond B, Lopez-Larrea C, Baranda FS, Menedez-Diaz MJ, Caillat-Zucman S, Beaurain G, Garchon HJ, Ilonen J, Reijonen H, Knip M, Boehm BO, Rosak C, Loliger C, Ottenhoff T, Contu L, Carcassi C, Savi M, Zanelli P, Neri M, Hamaguchi K, Kimura A, Dong RP, Chikiba N, Nagataki S, Gorodezky C, Debaz H, Robles C, Coimbra HB, Martinho A, Ruas MA, Sachs JA, Garcia-Pachedo M, Biro A, Nikaein A, Dombrausky L, Gonwa T, Zmijewsky C, Monos D, Kamoun M, Layrisse Z, Magli MC, Balducci P, Thorsby E. HLA class II associations in insulin-dependent diabetes mellitus among blacks, Caucasoids and Japanese. In: Tsuji K, Aizawa M, Sasazuki T, editors. HLA 1991: Proceedings of the 11th International Histocompatibility Workshop and Conference, Yokohama, Japan, 1991. Oxford: Oxford University Press, 1992: 713-722
20 **Ilonen J**, Koskinen S, Nejentsev S, Sjöroos M, Knip M, Schwartz EI, Adojaan B, Kovalchuk L, Sochnevs A. HLA-DQB1*0304-DRB1*0408 haplotype associated with insulin-dependent diabetes mellitus in populations in the eastern Baltic region. *Tissue Antigens* 1997; **49**: 532-534
21 **Van der Auwera BJ**, Schuit FC, Weets I, Ivens A, Van Autreve JE, Gorus FK. Relative and absolute HLA-DQA1-DQB1 linked risk for developing type I diabetes before 40 years of age in the Belgian population: implications for future prevention studies. *Hum Immunol* 2002; **63**: 40-50
22 **Bottini N**, Vang T, Cucca F, Mustelin T. Role of PTPN22 in type 1 diabetes and other autoimmune diseases. *Semin Immunol* 2006; **18**: 207-213
23 **Fife BT**, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev* 2008; **224**: 166-182
24 **Mosaad YM**, Elsharkawy AA, El-Deek BS. Association of CTLA-4 (+49A/G) gene polymorphism with type 1 diabetes mellitus in Egyptian children. *Immunol Invest* 2012; **41**: 28-37
25 **Nimri R**, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics* 2006; **117**: 2126-2131
26 **Doyle EA**, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004; **27**: 1554-1558
27 **American Diabetes Association**. Standards of medical care in diabetes--2010. *Diabetes Care* 2010; **33** Suppl 1: S11-S61
28 **Anaya JM**, Corena R, Abad V. Type 1 diabetes mellitus at the crossroad of polyautoimmunity. In: Walker SE, Jara LJ, editors. Endocrine Manifestations of Systemic Autoimmune Diseases. Handbook of Systemic Autoimmune Diseases. Johannesburg: Elsevier Ltd., 2008: 211-220
29 **Shapira Y**, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. *J Autoimmun* 2010; **34**: J168-J177
30 **Harrison LC**, Honeyman MC, Morahan G, Wentworth JM, Elkassaby S, Colman PG, Fourlanos S. Type 1 diabetes: lessons for other autoimmune diseases? *J Autoimmun* 2008; **31**: 306-310
31 **Concannon P**, Rich SS, Nepom GT. Genetics of type 1A diabetes. *N Engl J Med* 2009; **360**: 1646-1654
32 **Borchers AT**, Uibo R, Gershwin ME. The geoepidemiology of type 1 diabetes. *Autoimmun Rev* 2010; **9**: A355-A365
33 **Dorman JS**. Molecular epidemiology of insulin-dependent diabetes mellitus. *Epidemiol Rev* 1997; **19**: 91-98
34 **Lee HC**, Ikegami H, Fujisawa T, Ogihara T, Park SW, Chung YS, Park JO, Lee EJ, Lim SK, Kim KR, Huh KB, Kim YS, Lee DS, Kim DH. Role of HLA class II alleles in Korean patients with IDDM. *Diabetes Res Clin Pract* 1996; **31**: 9-15
35 **Katahira M**, Ishiguro T, Segawa S, Kuzuya-Nagao K, Hara I, Nishisaki T. Reevaluation of human leukocyte antigen DR-DQ haplotype and genotype in type 1 diabetes in the Japanese population. *Horm Res* 2008; **69**: 284-289
36 **Cinek O**, Kolousková S, Snajderová M, Sumník Z, Sedláková P, Drevínek P, Vavrinec J, Ronningen KS. HLA class II genetic association of type 1 diabetes mellitus in Czech children. *Pediatr Diabetes* 2001; **2**: 98-102
37 **Guja C**, Guja L, Nutland S, Rance H, Sebastien M, Todd JA, Ionescu-Tirgoviste C. Type 1 diabetes genetic susceptibility encoded by HLA DQB1 genes in Romania. *J Cell Mol Med* 2004; **8**: 249-256
38 **Hermann R**, Soltész G. [Predictive genetic screening for type-1 diabetes in the Hungarian population]. *Orv Hetil* 2004; **145**: 337-342
39 **Lambert AP**, Gillespie KM, Thomson G, Cordell HJ, Todd JA, Gale EA, Bingley PJ. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. *J Clin Endocrinol Metab* 2004; **89**: 4037-4043
40 **Altobelli E**, Blasetti A, Petrocelli R, Tumini S, Azzarone R, Tiberti S, Battistoni C, Merante D, Verrotti A, Fioroni MA, Iannarelli R, Poccia G, Papola F. HLA DR/DQ alleles and risk of type I diabetes in childhood: a population-based case-control study. *Clin Exp Med* 2005; **5**: 72-79
41 **Urcelay E**, Santiago JL, de la Calle H, Martínez A, Méndez J, Ibarra JM, Maluenda C, Fernández-Arquero M, de la Concha EG. Type 1 diabetes in the Spanish population: additional factors to class II HLA-DR3 and -DR4. *BMC Genomics* 2005; **6**: 56
42 **Buc M**, Bucová M, Javor J, Krivosíkova M, Stuchlíkova M, Shawkatova I, Michalková D, Barák L, Jancová E, Petrek M. Associations between HLA class II alleles and type 1 diabetes mellitus in the Slovak population. *Endocr Regul* 2006; **40**: 1-6
43 **Saruhan-Direskeneli G**, Uyar FA, Bas F, Günöz H, Bundak R, Saka N, Darendeliler F. HLA-DR and -DQ associations with insulin-dependent diabetes mellitus in a population of Turkey. *Hum Immunol* 2000; **61**: 296-302
44 **Eller E**, Vardi P, McFann KK, Babu SR, Yu L, Bugawan TL, Erlich HA, Eisenbarth GS, Fain PR. Differential effects of DRB1*0301 and DQA1*0501-DQB1*0201 on the activation and progression of islet cell autoimmunity. *Genes Immun* 2007; **8**: 628-633
45 **Ferreira AC**, Gomes KB, Sampaio IB, Oliveira VC, Pardini VC, Godard AL. Type 1 diabetes susceptibility determined by HLA alleles and CTLA-4 and insulin genes polymorphisms in Brazilians. *Arq Bras Endocrinol Metabol* 2009; **53**: 368-373
46 **Rojas-Villarraga A**, Botello-Corzo D, Anaya JM. HLA-Class II in Latin American patients with type 1 diabetes. *Autoimmun Rev* 2010; **9**: 666-673
47 **Manan H**, Angham AM, Sitelbanat A. Genetic and diabetic auto-antibody markers in Saudi children with type 1 diabetes. *Hum Immunol* 2010; **71**: 1238-1242
48 **Ei Wafai RJ**, Chmaisse HN, Makki RF, Fakhoury H. Associa-

tion of HLA class II alleles and CTLA-4 polymorphism with type 1 diabetes. *Saudi J Kidney Dis Transpl* 2011; **22**: 273-281
49 **Haider MZ**, Shaltout A, Alsaeid K, Qabazard M, Dorman J. Prevalence of human leukocyte antigen DQA1 and DQB1 alleles in Kuwaiti Arab children with type 1 diabetes mellitus. *Clin Genet* 1999; **56**: 450-456
50 **Stayoussef M**, Benmansour J, Al-Irhayim AQ, Said HB, Rayana CB, Mahjoub T, Almawi WY. Autoimmune type 1 diabetes genetic susceptibility encoded by human leukocyte antigen DRB1 and DQB1 genes in Tunisia. *Clin Vaccine Immunol* 2009; **16**: 1146-1150
51 **Al-Jenaidi FA**, Wakim-Ghorayeb SF, Al-Abbasi A, Arekat MR, Irani-Hakime N, Najm P, Al-Ola K, Motala AA, Almawi WY. Contribution of selective HLA-DRB1/DQB1 alleles and haplotypes to the genetic susceptibility of type 1 diabetes among Lebanese and Bahraini Arabs. *J Clin Endocrinol Metab* 2005; **90**: 5104-5109
52 **Kwon OJ**, Brautbar C, Weintrob N, Sprecher E, Saphirman C, Bloch K, Pinhas-Hamiel O, Assah S, Vardi P, Israel S. Immunogenetics of HLA class II in Israeli Ashkenazi Jewish, Israeli non-Ashkenazi Jewish, and in Israeli Arab IDDM patients. *Hum Immunol* 2001; **62**: 85-91
53 **Gaber SA**, Mazzola G, Berrino M, Canale L, Cornaglia M, Ghali I, Sergio Curtoni E, Amoroso A. Human leukocyte antigen class II polymorphisms and genetic susceptibility of IDDM in Egyptian children. *Diabetes Care* 1994; **17**: 1341-1344
54 **Lucotte G**, Mercier G. Brief communication: Y-chromosome haplotypes in Egypt. *Am J Phys Anthropol* 2003; **121**: 63-66
55 **Badran WA**, Fahmy I, Abdel-Megid WM, Elder K, Mansour R, Kent-First M. Length of androgen receptor-CAG repeats in fertile and infertile Egyptian men. *J Androl* 2009; **30**: 416-425
56 **Hermann R**, Mijovic CH, Rayner M, Croft N, Kelly MA, Jenkins D, Soltész G, Barnett AH. HLA alleles and IDDM in children in Hungary: a comparison with Finland. *Hum Immunol* 2001; **62**: 391-398
57 **Todd JA**. Etiology of type 1 diabetes. *Immunity* 2010; **32**: 457-467
58 **Price P**, Cheong KY, Boodhoo A, Witt CS, McCann V, Christiansen FT, Allcock RJ. Can MHC class II genes mediate resistance to type 1 diabetes? *Immunol Cell Biol* 2001; **79**: 602-606
59 **Rønningen KS**, Bangstad HJ, Undlien DE, Thorsby E. Influence of genetic factors (HLA class II genes, insulin-gene region polymorphisms) and metabolic control on the development of diabetic nephropathy. *Diabetes Res* 1993; **23**: 31-40

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CASE REPORT

Hyperinsulinemia and insulin resistance in a patient with type 2 diabetes complicated with myelofibrosis

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Abstract

Inflammation induces insulin resistance and hyperinsulinemia due to elevation of serum cytokines such as tumor necrosis factor-α and interleukins. Chronic myeloproliferative diseases including myelofibrosis show higher serum interleukin levels than healthy subjects, which has been suggested to be the useful markers for disease activity. However, an association between myelofibrosis and insulin resistance has not ever been discussed anywhere. Here we report a case of type 2 diabetes showing remarkable hyperinsulinemia and insulin resistance possibly due to myelofibrosis.

Key words: Cytokines; Hepatosplenomegaly; Hyperinsulinemia; Insulin resistance; Myelofibrosis

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INTRODUCTION

Chronic inflammation induces insulin resistance and hyperinsulinemia due to elevation of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukins[1]. Chronic myeloproliferative diseases show higher serum interleukin levels than healthy subjects, recently, which has been suggested to be the useful clinical markers for disease activity of myeloproliferative diseases[2]. However, an association between chronic myeloproliferative diseases including myelofibrosis and insulin resistance has not ever been discussed anywhere. Here we report a case with type 2 diabetes showing hyperinsulinemia and insulin resistance possibly due to myelofibrosis.

CASE REPORT

A 71-year-old man was diagnosed as having type 2 diabetes and myelofibrosis in 1998 and 2001, respectively. His diabetes was treated by α-glucosidase inhibitor, voglibose (0.6 mg/d) from 1998 to 1999, and his HbA1c levels were 7.0%-7.7%. He was treated by nateglinide (270 mg/d) from 1999 to 2003, and his HbA1c levels were 6.5%-7.4%. After the basal supported oral therapy using nateglinide (270 mg/d) and 4-5 units of NPH-insulin (from 2003-2004) and insulin glargine (from 2004) at bedtime, his HbA1c levels were 6.0%-6.9%. Recently, his diabetes has been treated by using nateglinide (270 mg/d) and 4 units of insulin glargine at bedtime. His myelofibrosis progressed since June, 2011, and the counts of leukocyte and platelets were 2000/μL and 2.8×10^4/μL, respectively, and hemoglobin concentration was 73 g/L on July 1, 2011. At the same time, his blood glucose control became

worse. His plasma glucose and HbA1c were 1500 mg/L and 5.8%, respectively, on July 1, 2011. In September, 2011, fasting plasma glucose and HbA1c levels increased to 2020 mg/L and 7.2%, respectively. He was admitted to our hospital. His body height, body weight and body mass index were 169 cm, 56 kg and 19.6 kg/m^2, respectively. We started the intensive insulin therapy, and his blood glucose levels were 1460-2480 mg/L by using 10, 8 and 10 units of insulin aspart before breakfast, lunch and dinner, respectively, and 8 units of insulin glargine at bedtime, showing a significantly increased requirement of insulin dose. However, unexpectedly, his urinary C-peptide level was remarkably elevated (248 μg/d; normal, 29.2-167 μg/d). Anti-insulin antibody (^{125}I-insulin binding rate, 1.5%; normal, < 0.4%) level was slightly elevated, and anti-insulin receptor antibody was not detected. Abdominal computed tomography showed severe hepatosplenomegaly. We measured his serum inflammatory cytokines. Serum levels of TNF-α (6.3 pg/mL; normal, 0.6-2.8 pg/mL), interleukin-1 (11 pg/mL; normal, < 10 pg/mL) and interleukin-6 (5.9 pg/mL; normal, < 4.0 pg/mL) were significantly elevated. However, interleukin-2 (0.8 U/mL; normal, < 0.8 U/mL) and interleukin-8 (< 2.0 pg/mL; normal, < 2.0 pg/mL) were not elevated.

DISCUSSION

Myelofibrosis is myeloproliferative disease which induces fibrosis of the bone marrow and leads to hepatosplenomegaly, which may cause portal hypertension and portosystemic shunt[3]. To our knowledge, the association between myelofibrosis and hyperinsulinemia in humans has not ever been studied. The insulin metabolism in rats with portal hypertension has been previously reported[4]. The metabolic clearance rate of insulin in the portal-hypertensive rats was significantly reduced in comparison with the control rats[4]. The control of blood glucose levels when he was diagnosed as having diabetes is dealt with the long-term influence of early metabolic control on clinical outcomes, also known as "metabolic memory", and where a long-term receptor for advanced glycation end products activation is a crucial element in the maintenance of a low-grade systemic chronic inflammation, which is a very well-known feature of diabetes mellitus[5,6]. His plasma glucose control was poor (HbA1c, 6.5%-7.7%) from 1998 to 2003, before the start of the basal supported oral therapy using nateglinide and insulin. We have to mention that early poor glycemic environment might also possibly affect his diabetes aggravation.

We also have to mention that we should have measured cytokine levels on this patient before the onset of the acute progress on June 2011, and we used the cut-off values for cytokines from healthy individuals, however, comparisons should be made in reference to cytokines serum levels on tightly controlled diabetic patients.

In conclusion, the decrease of insulin clearance due to portosystemic shunt, and elevated serum levels of TNF-α interleukin-1 and interleukin-6, strongly associated with insulin resistance[1], may induce hyperinsulinemia and insulin resistance in our patient with type 2 diabetes complicated with myelofibrosis.

REFERENCES

1 **Shoelson SE**, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; **116**: 1793-1801

2 **Panteli KE**, Hatzimichael EC, Bouranta PK, Katsaraki A, Seferiadis K, Stebbing J, Bourantas KL. Serum interleukin (IL)-1, IL-2, sIL-2Ra, IL-6 and thrombopoietin levels in patients with chronic myeloproliferative diseases. *Br J Haematol* 2005; **130**: 709-715

3 **Abu-Hilal M**, Tawaker J. Portal hypertension secondary to myelofibrosis with myeloid metaplasia: a study of 13 cases. *World J Gastroenterol* 2009; **15**: 3128-3133

4 **Sikuler E**, Polio J, Groszmann RJ, Hendler R. Glucagon and insulin metabolism in a portal-hypertensive rat model. *Am J Physiol* 1987; **253**: G110-G115

5 **LeRoith D**, Fonseca V, Vinik A. Metabolic memory in diabetes--focus on insulin. *Diabetes Metab Res Rev* 2005; **21**: 85-90

6 **Lanati N**, Emanuele E, Brondino N, Geroldi D. Soluble RAGE-modulating drugs: state-of-the-art and future perspectives for targeting vascular inflammation. *Curr Vasc Pharmacol* 2010; **8**: 86-92

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Events Calendar 2012

January 15-17, 2012
ICADIT 2012: International conference on Advances in Diabetes and Insulin Therapy
Zurich, Switzerland

January 29-February 3, 2012
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Santa Fe, NM, United States

February 3, 2012
The Future of Obesity Treatment
London, United Kingdom

February 8-11, 2012
5th International Conference on Advanced Technologies and Treatments for Diabetes
Barcelona, Spain

February 9-10, 2012
EC Conference on Diabetes and Obesity Research - Save the Date
Brussels, Belgium

February 21, 2012
Association of Children's Diabetes Clinicians 6th Annual Meeting
Coventry, United Kingdom

February 23, 2012
Diabetes and kidney disease: advances and controversies
Birmingham, United Kingdom

March 1-3, 2012
International conference on Nutrition and Growth
Paris, France

March 7-9, 2012
Diabetes UK Annual Professional Conference 2012
Glasgow, United Kingdom

March 15 -16, 2012
Monogenic Disorders of Insulin Secretion: Congenital Hyperinsulinism and Neonatal Diabetes
Philadelphia, PA, United States

March 15 -17, 2012
2012 DF Con - Diabetic Foot Global Conference
Hollywood, CA, United States

March 19-22, 2012
Society for Endocrinology BES 2012
Harrogate, United Kingdom

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Rio de Janeiro, Brazil

March 29-31, 2012
The 4th International Conference on Advances in Diabetes and Insulin Therapy
Riga, Latvia

March 29-April 1, 2012
New Frontiers in Diabetes Management
Ocho Rios, Jamaica

April 2-6, 2012
6th Annual Primary Care Spring Conference: Session 1
Palm Coast, FL, United States

April 4-7, 2012
39th Panhellenic Congress of Endocrinology and Metabolism
Athens, Greece

April 11-13, 2012
ICDM 2012: International Conference on Diabetes and Metabolism
Venice, Italy

April 11-13, 2012
ICDHLSP 2012: International Conference on Diabetes, Hypertension, Lipids and Stroke Prevention
Venice, Italy

April 16-17, 2012
Paediatric and Adolescent Diabetes
Birmingham, United Kingdom

April 22-25, 2012
9th International Podocyte Conference
Miami, FL, United States

May 9-12, 2012
19th European Congress on Obesity
Lyon, France

May 23-27, 2012
AACE 21st Annual Scientific and Clinical Congress - American Association of Clinical Endocrinologists
Philadelphia, PA, United States

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48th European Association for the Study of Diabetes Annual Meeting
Berlin, Germany

November 7-9, 2012
40th Meeting of the British Society for Paediatric Endocrinology and Diabetes
Leeds, United Kingdom

November 8-11, 2012
The 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
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INSTRUCTIONS TO AUTHORS

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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Issue with no volume

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

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Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 200201 03498. 2002 Aug 1

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