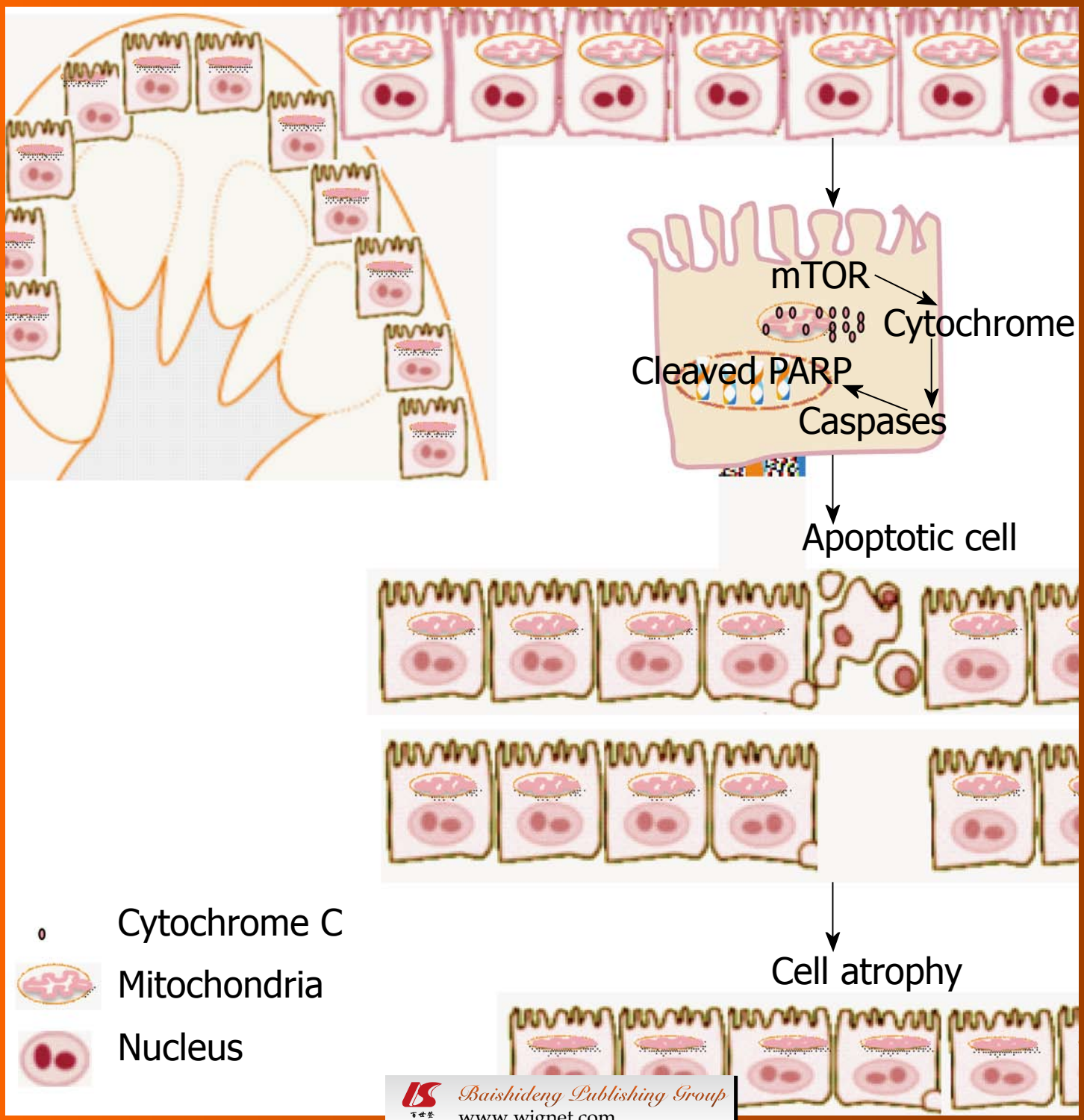
ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2013 April 15; 4(2): 14-46



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A peer-reviewed, online, open-access journal of diabetes

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World Journal of Diabetes

Contents

Bimonthly Volume 4 Number 2 April 15, 2013

Contents

World Journal of Diabetes
Volume 4 Number 2 April 15, 2013

AIM AND SCOPE

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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INDEXING/ ABSTRACTING

World Journal of Diabetes is now indexed in PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
April 15, 2010

FREQUENCY
Bimonthly

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Xiu-Xia Song, Vice Director
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http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
April 15, 2013

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-9358/g_info_20100107165233.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
wjd@wjgnet.com
doi:10.4239/wjd.v4.i2.14

World J Diabetes 2013 April 15; 4(2): 14-18
ISSN 1948-9358 (online)

FIELD OF VISION

Bariatric surgery as a treatment option in patients with type 2 diabetes mellitus

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Received: December 23, 2012 Revised: February 10, 2013
Accepted: March 6, 2013
Published online: April 15, 2013

Abstract

Type 2 diabetes mellitus (T2DM) is a leading cause of blindness, non-traumatic amputation and end-stage renal disease as well as a major cardiovascular risk factor. Tight glycemic control reduces the incidence of microvascular complications of T2DM whereas its effects on macrovascular complication are more controversial. However, glycemic targets are achieved by a minority of diabetic patients despite the availability of several antidiabetic agents. In the present commentary, we discuss the findings of two recent randomized studies that compared bariatric surgery with medical treatment in patients with uncontrolled T2DM. Both studies showed that bariatric surgery results in remission of T2DM in the majority of patients. However, both studies were limited to relatively young patients without comorbidities, had relatively short follow-up and did not assess the effects of surgery on T2DM complications. Moreover, the perioperative complications of bariatric surgery and its limited availability in some areas are additional barriers to the wider implementation of this therapeutic approach. On the other hand, the elucidation of the mechanisms underpinning the resolution of T2DM following bariatric surgery might result in the development of novel, more effective pharmacotherapies for this common disease.

Key words: Type 2 diabetes mellitu; Bariatric surgery; Roux-en-Y gastric bypass; Biliopancreatic diversion; Sleeve gastrectomy; Adjustable gastric banding

Core tip: In the present commentary, we discuss the findings of two recent randomized studies that compared bariatric surgery with medical treatment in patients with uncontrolled type 2 diabetes mellitus (T2DM). Both studies showed that bariatric surgery results in remission of T2DM in the majority of patients. However, both studies were limited to relatively young patients without comorbidities, had relatively short follow-up and did not assess the effects of surgery on T2DM complications.

Spanou M, Tziomalos K. Bariatric surgery as a treatment option in patients with type 2 diabetes mellitus. *World J Diabetes* 2013; 4(2): 14-18 Available from: URL: http://www.wjgnet.com/1948-9358/full/v4/i2/14.htm DOI: http://dx.doi.org/10.4239/wjd.v4.i2.14

COMMENTARY ON HOT TOPICS

Type 2 diabetes mellitus (T2DM) has become a global epidemic in the recent decades[1]. Diabetes mellitus affects 346 million people worldwide and T2DM accounts for 90% of the cases[1]. Moreover, T2DM is a leading cause of blindness, non-traumatic amputation and end-stage renal disease as well as a major risk factor for cardiovascular disease[1].

Tight glycemic control reduces the risk for the microvascular complications of T2DM whereas its effects on macrovascular complications are more controversial[2-8].

Methods to achieve glycemic control include lifestyle changes (diet and exercise) and pharmacotherapy with either oral or injectable agents, the latter primarily including insulin[9]. However, glycemic control progressively deteriorates during treatment with oral agents in the majority of patients as a result of the progressive decline in insulin secretion from pancreatic beta cells[10]. In addition, glycemic targets are achieved by a small minority of patients even in specialist centers[11,12]. Moreover, tight glycemic control is associated with increased risk for hypoglycemia and weight gain, resulting in decreased adherence to treatment, which in turn further worsens glycemic control[5-8]. In turn, suboptimal glycemic control is associated with increased risk for complications, particularly nephropathy and retinopathy[2,4,5].

Given the limited efficacy of existing antidiabetic agents in achieving glycemic targets, bariatric surgery has been evaluated for the management of severely obese patients with T2DM and yielded promising results in uncontrolled studies[13]. Recently, two studies compared bariatric surgery with medical treatment in patients with uncontrolled T2DM[14,15]. In the first study, Mingrone *et al*[14] evaluated two types of bariatric surgery, laparoscopic Roux-en-Y gastric bypass and open biliopancreatic diversion, in patients 30-60 years-old with a body mass index (BMI) $\geqslant$ 35 kg/m^2, who had T2DM for $\geqslant$ 5 years and hemoglobin A1c (HbA1c) levels $\geqslant$ 7%. Patients with type 1 diabetes mellitus, severe diabetes complications, other severe medical conditions or previous bariatric surgery were excluded from the study[14]. Sixty patients were randomly assigned into three treatments: Roux-en-Y gastric bypass, biliopancreatic diversion and medical treatment (lifestyle modification, oral hypoglycemic agents and/or insulin)[14]. The primary endpoint was the rate of remission of T2DM at 2 years, defined as fasting plasma glucose levels < 100 mg/dL (5.6 mmol/L) and HbA1c levels < 6.5% for at least 1 year without pharmacologic treatment[14]. Diabetes remission was achieved at 2 years in 75 and 95% of patients who had undergone gastric bypass and biliopancreatic diversion, respectively. None of the patients assigned to medical treatment achieved T2DM remission ($P < 0.001$ *vs* both surgery groups)[14]. Age, sex, baseline BMI, diabetes duration and weight change did not predict T2DM remission[14]. Weight loss was similar in the two surgical groups (approximately 33%) and smaller in the medical treatment group (4.7%)[14]. Regarding other cardiovascular risk factors, serum low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels showed a similar reduction in the medical treatment and gastric bypass groups but decreased more in the biliopancreatic diversion group[14]. In contrast, serum high density lipoprotein cholesterol (HDL-C) levels showed a similar increase in the medical treatment and biliopancreatic diversion groups but increased more in the gastric bypass group[14]. Blood pressure (BP) decreased and the number of antihypertensive agents was reduced to a comparable extent in the three groups[14].

In the second study, Schauer *et al*[15] compared intensive medical treatment alone and intensive medical treatment combined with either laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy in 150 patients 20-60 years old with a BMI between 27 and 43 kg/m^2, and with HbA1c levels > 7%. Patients with uncontrolled medical or psychiatric disorders or previous bariatric or complex abdominal surgery were excluded from the study[15]. The primary endpoint, the rate of patients with HbA1c levels $\leqslant$ 6% at 12 mo with or without antidiabetic medications, was achieved in 42% of patients who underwent gastric bypass, in 37% of patients who underwent sleeve gastrectomy and in 12% of patients in the medical treatment group ($P = 0.002$ and $P = 0.008$ for the comparison between medical treatment with gastric bypass and sleeve gastrectomy, respectively)[15]. Age, baseline BMI, diabetes duration and use of insulin did not predict the primary outcome[15]. Percentage weight loss was greater with gastric bypass than with sleeve gastrectomy (27.5% and 24.7%, respectively; $P = 0.02$) whereas patients assigned to medical treatment lost less weight (5.2%; $P < 0.001$ *vs* both surgical groups)[15]. In both surgical groups, serum high sensitivity C-reactive protein levels decreased and HDL-C levels increased compared with the medical treatment group[15]. In contrast, serum TG levels decreased only in the gastric bypass group compared with the medical treatment group[15]. Serum LDL-C levels and BP did not differ among groups after 12 mo but the use of lipid-lowering and antihypertensive medications declined significantly only in the surgical groups[15].

Overall, both studies suggest that bariatric surgery is more effective in achieving glycemic control than medical treatment and results in T2DM remission (*i.e.,* no need for antidiabetic medications) in a sizeable proportion of patients[14,15]. The higher remission rates in the study by Pournaras *et al*[16] might be due to differences in operative technique and the less stringent criteria for defining remission, the longer follow-up or the shorter duration of T2DM; on the other hand, the smaller sample size suggests the possibility of a type 1 statistical error[14,15]. In both studies, other cardiovascular risk factors, including dyslipidemia and hypertension, also improved substantially after bariatric surgery[14,15]. Importantly, the benefits of bariatric surgery appeared to be independent of the preoperative BMI[14,15] and, in the study by Schauer *et al*[15], to apply not only to patients with BMI > 35 kg/m^2 but also to those with BMI 27-35 kg/m^2. This finding suggests that current recommendations that propose bariatric surgery only for patients with T2DM with BMI > 35 kg/m^2 might need to be modified[17]. The benefits of bariatric surgery were also independent of age (within the age range of 20-60 years-old)[14,15]. Diabetes remission rates were also independent of diabetes duration[14,15] whereas previous retrospective studies reported that patients with longer-lasting T2DM show lower rates of T2DM resolution after bariatric surgery[18]. Therefore, this finding should be interpreted with caution because both studies were rather small and probably underpowered to detect an association between T2DM remission rates and dia-

betes duration[14,15] and also because the variability of T2DM duration was very small in the study by Mingrone *et al*[14] (mean duration, 6.0 ± 1.1 years). The findings of these trials are in agreement with previous uncontrolled studies that reported resolution of T2DM in 65%-83% of patients[13,18-22] and with a smaller study in 60 diabetic patients with BMI 30-40 kg/m^2 where laparoscopic adjustable gastric banding and medical treatment resulted in T2DM remission in 73% and 13% of patients, respectively[23]. In addition, these benefits add to the other positive effects of bariatric surgery including remission of other obesity-associated comorbidities such as hypertension, dyslipidemia, metabolic syndrome, chronic kidney disease, left ventricular hypertrophy, non-alcoholic fatty liver disease and obstructive sleep apnea[24,25]. Preliminary data from uncontrolled studies also suggest a reduction in cancer rates following bariatric surgery[26,27]. Bariatric surgery also appears to reduce the risk of T2DM in obese patients[28]. However, it should be noted that other studies did not show a beneficial effect of bariatric surgery on obesity-related comorbidities, including non-alcoholic fatty liver disease and obstructive sleep apnea[29,30].

Is therefore bariatric surgery an alternative option for patients with T2DM? Probably not yet, for both medical and logistic reasons. First, bariatric surgery is infrequently associated with both short- and long-term complications, including mortality, even in experienced centers[31]. In the two described studies, there were no perioperative deaths but 6 patients (4.3%) required reoperation[14,15]. However, these studies were small, had a relatively short-term follow-up and were performed in experienced centers[14,15]. Perioperative mortality rates of bariatric surgery range between 0.10% and 0.35%[31]. Non-fatal perioperative complications, including anastomotic and staple line leaks, wound infections, pulmonary embolism and hemorrhage occur at higher rates (1.7%-3.1%) even though they are progressively becoming less frequent, mainly as a result of higher hospital volumes[32,33]. Second, it is still unclear whether bariatric surgery reduces cardiovascular events, even though uncontrolled studies suggested a cardiovascular morbidity and mortality benefit[26,34,35]. Third, existing randomized studies excluded patients with comorbidities and those older than 60 years, who constitute the majority of patients with T2DM[14,15]. Finally, the lack of experienced surgeons in many areas and the cost of bariatric surgery are additional barriers to the wider implementation of this treatment, even though the cost of bariatric surgery might compare favorably with the costs of the lifelong management of diabetes and of its micro- and macrovascular complications[36-38].

In conclusion, bariatric surgery might be considered in relatively young patients with uncontrolled T2DM despite adequate pharmacological treatment, without comorbidities, and with BMI > 35 kg/m^2. Current guidelines state that bariatric surgery may be considered for adults with BMI ⩾ 35 kg/m^2 and T2DM, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy (level of evidence B)[17]. They also state that there is currently insufficient evidence to generally recommend surgery in patients with BMI < 35 kg/m^2 outside of a research protocol (level of evidence E)[17]. Even though existing guidelines do not mention specific contraindications for bariatric surgery, it is clear that the risk of peri- and postoperative complications should be balanced against the benefits of bariatric surgery[17]. However, given the high and rising prevalence of T2DM as well as the lack of long-term data on safety and efficacy of bariatric surgery, this treatment will probably have limited impact on the T2DM epidemic. On the other hand, weight loss cannot entirely explain the beneficial effects of bariatric surgery because these occur soon after the operation and before maximum weight loss is achieved[13-15]. Changes in the bioavailability of gut hormones, fat malabsorption and improvement of insulin resistance might also play a role[39-45]. In contrast, the exclusion of proximal small intestine does not appear to contribute to the improvement in glucose homeostasis[45]. On the other hand, accumulating data suggest that newer classes of antidiabetic agents, including thiazolidinediones and incretin-based agents, might delay the decline in beta cell function by alleviating glucolipotoxicity[46]. Recent data suggest that bariatric surgery also has a beneficial effect on beta cell function[44]. The extensive discussion of the mechanisms involved in the remission of T2DM after bariatric surgery is beyond the scope of this commentary; several comprehensive reviews on the topic have been published recently[47,48]. The elucidation of the pathophysiologic mechanisms underpinning the resolution of T2DM and other obesity-associated comorbidities after bariatric surgery might lead to the development of novel and more effective pharmacotherapies for these common diseases.

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P- Reviewers Barnett A, Guerrero-Romero F
S- Editor Zhai HH **L- Editor** A **E- Editor** Li JY

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
wjd@wjgnet.com
doi:10.4239/wjd.v4.i2.19

World J Diabetes 2013 April 15; 4(2): 19-26
ISSN 1948-9358 (online)

TOPIC HIGHLIGHT

J Fernando Arevalo, MD, *Series Editor*

Bevacizumab for the management of diabetic macular edema

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Received: October 24, 2012 Revised: February 15, 2013
Accepted: March 23, 2013
Published online: April 15, 2013

Abstract

Diabetic retinopathy (DR) is a leading cause of vision loss in the working-age population and is relatedto 1%-5% of cases of blindness worldwide. Diabetic macular edema (DME) is the most frequent cause of DR vision loss and is an important public health problem. Recent studies have implicated vascular endothelial growth factor (VEGF) in DR and DME pathogenesis, as well as provided evidence of the benefits of anti-VEGF agents for the management of such conditions. Despite the benefits of intravitreal ranibizumab injection for the management of DME, the cost-effectiveness of intravitreal bevacizumab therapy has gained increasing interest in the scientific community. This review summarizes the studies examining bevacizumab for the management of DME, focusing on the efficacy and duration of the clinical benefits of decreasing DME and the improvement of best-corrected visual acuity (BCVA). There is strong evidence that intravitreal bevacizumab injection therapy has a good cost-effective profile in the management of DME and may be associated with laser photocoagulation; however, its clinical superiority in terms of the duration of DME regression and the improvement of BCVA compared with intravitreal ranibizumab and other intravitreal anti-VEGF therapies remains unclear and deserves further investigation.

Key words: Diabetic macular edema; Bevacizumab; Anti-vascular endothelial growth factor; Diabetic retinopathy

Core tip: This review summarizes the studies examining bevacizumab for the management of diabetic macular edema (DME), focusing on the efficacy and duration of the clinical benefits of decreasing DME and the improvement of best-corrected visual acuity.

Stefanini FR, Arevalo JF, Maia M. Bevacizumab for the management of diabetic macular edema. *World J Diabetes* 2013; 4(2): 19-26 Available from: URL: http://www.wjgnet.com/1948-9358/full/v4/i2/19.htm DOI: http://dx.doi.org/10.4239/wjd.v4.i2.19

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of vision loss in working-age patients around the world. DR is related to 1% of all cases of blindness worldwide, and it may be related to 5% of blindness in some countries[1,2] (Figure 1). The main cause of vision impairment in diabetic patients is diabetic macular edema (DME)[3-5]. DME may occur at any stage of non-proliferative or proliferative DR[6,7]. Macular edema is divided into two types: focal and diffuse. Focal macular edema is caused by focal leak-

age from microaneurysms and dilated retinal capillaries with abnormal permeability. Complete or partial rings, as a circinate pattern of hard exudates, often demarcate the macular edema[8] (Figure 2A). In diffuse macular edema, generalized leakage from dilated capillaries is observed throughout the posterior pole (Figure 2B). Occlusion of a portion of the capillary bed causes dilation of the patent capillaries, which tend to leak, leading to edema[9]. The risk factors associated with diffuse macular edema are systemic hypertension, adult-onset diabetes mellitus and poor blood glucose control, cardiovascular disease, impaired renal function, increased number of retinal microaneurysms, advanced retinopathy and vitreomacular traction[9,10]. It is estimated that DME occurs in 3% to 6% of all patients with diabetes aged 18 or older[11]. A large epidemiological study indicated that macular edema was present in 26% of the study patients with DR[12].

The most efficient tool for preventing vision loss from DR is screening and identification of at-risk patients, along with regular office visits to educate patients on the importance of tight blood sugar and blood pressure control in both type 1 and type 2 diabetes[3].

Once a patient develops DME, the gold standard treatment in recent decades has been macular photocoagulation (MPC) using the laser technique, which reduces the risk of moderate visual loss by approximately 50% (Figure 3)[13]. A review of the data from the Early Treatment DR Study (ETDRS) demonstrated that approximately 40% of the patients who demonstrated improvement with focal laser treatment and a baseline best-corrected visual acuity (BCVA) worse than 20/40 had gained 6 or more letters at 3-year post follow-up[13,14]. Recently, the Diabetic Retinopathy Clinical Research Network (DRCR.net) has demonstrated BCVA improvement of more than 5 letters of vision in 51%, 47% and 62% of eyes treated with MPC after 1, 2 and 3 years of follow-up, respectively[5,15-17].

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS AND DME

In recent years, alternative or adjunct treatments for DME have been studied, and various pharmacological compounds are under investigation, such as intravitreal triamcinolone acetonide (IVTA) and therapies using inhibitors of vascular endothelial growth factor (VEGF)[4]. Studies performed by DRCR.net demonstrated that despite the early benefits of intravitreal injection of 4 mg of triamcinolone acetonide (TA), the BCVA and retinal thickening at 4 mo compared with a 1-mg TA dose or with focal/grid photocoagulation, the final mean BCVA at 2 and 3 years was better in the MPC group[15,16].

VEGF expression and signaling are deregulated in DR, and VEGF is an important mediator of blood retinal barrier breakdown, which leads to fluid leakage below the macula and the development of macular edema. Therefore, at present, treatment with anti-VEGF agents is one of the most promising approaches for the treatment of vision loss due to DME[18,19]. Several studies have been conducted that have addressed the efficacy and safety of anti-VEGF agents, including ranibizumab (Lucentis, Genentech, Inc., United States), pegaptanib (Macugen, OSI/Eyetech, United States), and aflibercept (EYLEA; Regeneron, United States) and bevacizumab (Avastin, Genentech, Inc., United States), in the treatment of DME.

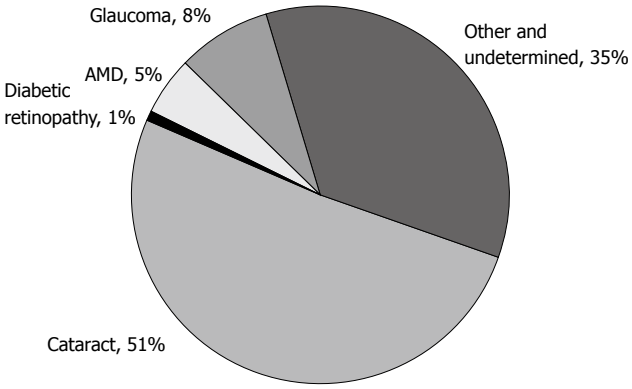

Figure 1 Pie chart displaying the distribution of global causes of blindness. Although cataracts are responsible for more than half of the cases, they are potentially reversible. When considering the causes of permanent vision impairment, diabetic retinopathy contributes significantly to 1%-5% of cases of blindness. In addition, diabetic retinopathy is the major cause of irreversible blindness in the working-age patients worldwide. AMD: Age-related macular disease.

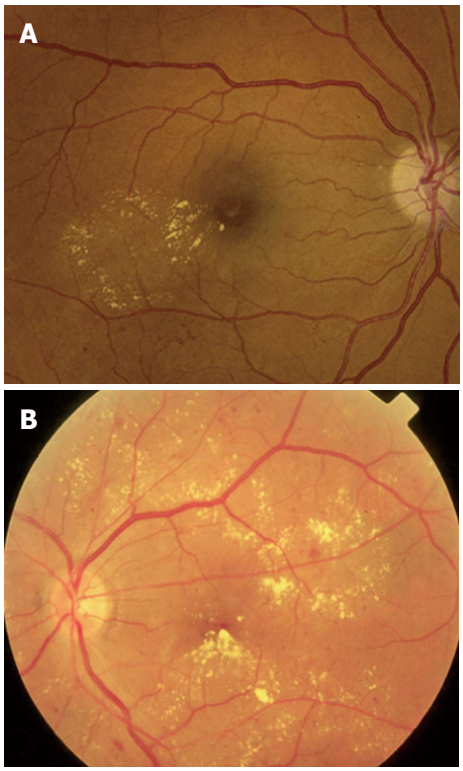

Figure 2 Clinical patterns of diabetic macular edema. A: Focal macular edema marked by focal leakage from microaneurysms and dilated retinal capillaries with abnormal permeability, making a complete ring as a localized circinate pattern of hard exudates; B: Diffuse macular edema, characterized by hard exudates with generalized leakage from dilated capillaries throughout the posterior pole.

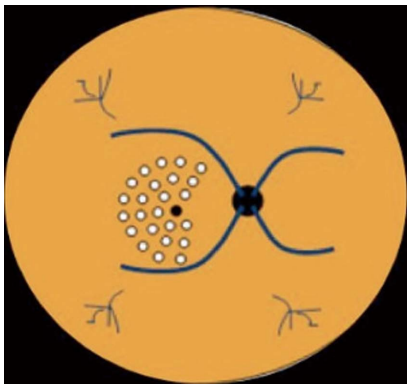

Figure 3 Macular area treated by laser photocoagulation using the scheme proposed by the Early Treatment Diabetic Retinopathy Study.

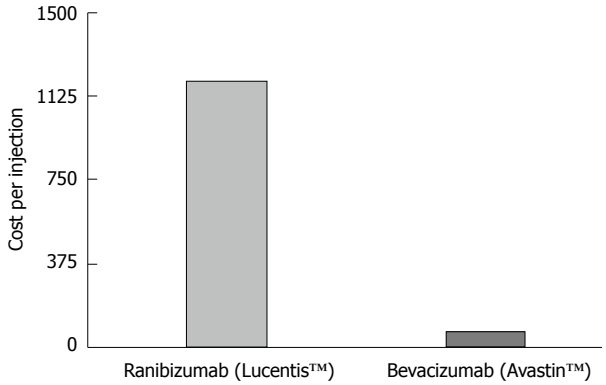

Figure 4 Cost per injection of ranibizumab (LucentisTM Genentech, United States), in the treatment of diabetic macular edema, compared with the cost per injection of bevacizumab (Avastin, Roche, United States). The cost is, in average, 20-fold higher in for treatment with ranibizumab than bevacizumab. Depending on the country, this difference may vary from 20× to 50×.

It has been shown that pegaptanib inhibits VEGF permeability effects[20,21]. The VEGF Inhibition Study in Ocular Neovascularization trial established the safety and efficacy in neovascular age-related macular disease (AMD)[22]. For DME, the efficacy and safety of 0.3 mg of pegaptanib sodium *vs* sham injections was studied in a phase-2/3, multicenter, randomized, double-blinded trial[23]. After 102 wk, the pegaptanib group presented significantly better results than the sham injection group in BCVA change, letters gained and reduced need for focal/grid laser photocoagulation.

Recently, 2 mg/0.05 mL aflibercept (EYLEA; Regeneron, United States) received regulatory approval from the Food and Drug Administration (FDA) for the treatment of neovascular AMD. For management of DME, a multicenter, randomized, double-masked, phase-2 clinical trial, the DA VINCI Study, tested different dosing regimens of aflibercept (VEGF Trap-Eye) and compared them with laser photocoagulation: 0.5 mg every 4 wk, 2 mg every 4 wk, 2 mg for the 3 initial doses then every 8 wk, 2 mg for the 3 initial doses then as needed. Subjects in the VEGF Trap-Eye groups experienced mean reductions in central retina thickness and, at their 6-mo follow-up, had better results for BCVA than those who were treated with laser photocoagulation. However, it is important to note that a considerable number of re-injections were necessary.

The drug was well tolerated. The phase-3 trials on aflibercept in patients with visual loss due to DME are ongoing[7,24].

Ranibizumab is approved for the treatment of neovascular AMD and just received FDA approval (August 2012) for the treatment of visual impairment due to DME, based on the RIDE and RISE clinical trials. Several clinical trials have been performed examining the use of ranibizumab for the treatment of visual impairment due to DME. The RESTORE study demonstrated superiority after 12 mo of ranibizumab monotherapy (0.5 mg) administered as needed or as an adjunct to laser photocoagulation *vs* laser monotherapy[25,26]. The READ-2 study found that ranibizumab (0.5 mg) alone or in combination with laser photocoagulation improved BCVA over 2 years in DME patients[27]. RIDE and RISE, two identicallydesigned, parallel, double-blinded, 3-year clinical trials that were sham-treatment controlled for 24 mo had preliminary results that demonstrated that patients who received 0.3 mg of ranibizumab experienced significant, early and sustained improvements in vision. The DRCR.net conducted a study to investigate the role of ranibizumab and also steroid treatment combined with laser photocoagulation. The 2-year results of this study indicated that 0.5 mg of ranibizumab administered as needed and combined with laser therapy produced a rapid and sustained improvement in the BCVA of patients with DME compared with laser treatment[28].

BEVACIZUMAB FOR DME

Bevacizumab is a full-size, humanized, recombinant monoclonal immunoglobulin G antibody that inactivates all VEGF isoforms. It is approved as an anti-VEGF agent for the systemic treatment of metastatic colorectal cancer, but its use for ocular diseases is off-label. Intravitreal bevacizumab (IVB) has been more widely utilized, primarily dueto its low cost, safety and positive clinical effects in case studies and retrospective studies (Figure 4)[29-31]. The widespread use of IVB for the exudative form of AMD as well as the evidence of positive clinical effects in the management of DME[28,32,33] have resulted in the formal evaluation of its safety and efficacy in the management of DME[34].

RESULTS AND DISCUSSION

The DRCR.net conducted a randomized study of 121 eyes over a 12-wk period[33]. It consisted of five treatment arms: (1) focal photocoagulation; (2) two intravitreal injections of 1.25 mg of bevacizumab at 0 and 6 wk; (3) two intravitreal injections of 2.5 mg of bevacizumab at 0 and 6 wk; (4) 1.25 mg of bevacizumab at week 0 followed by a sham injection at 6 wk; and (5) 1.25 mg of bevacizumab at 0 and 6 wk combined with focal photocoagula-

tion at 3 wk. The majority of eyes, 69%, were refractory to previous treatment for DME. The eyes of two groups that received two bevacizumab injections without laser, 2 and 3, had a significant BCVA improvement over the laser-only group 1, and this difference persisted through the 12 wk. These two groups also had a greater improvement in central subfield thickness at the 3-wk visit. No differences were observed between groups 2 and 3 (1.25-mg and 2.5-mg doses, respectively). The single injection group had no advantage over the photocoagulation group in this study. Group 5, which combined bevacizumab with photocoagulation, had results comparable with laser-only treatment. This study suggested that bevacizumab was an effective drug for the management of DME as a primary treatment and also for refractory eyes. Safety data were reported for 24 wk, and no safety concerns were detected. Two trends were identified: (1) the eyes that received primary treatment had greater improvement ($P = 0.04$) than the refractories; and (2) the presence of subretinal fluid at the initial therapy [measured by optical coherence tomography (OCT)] may be associated with a greater improvement in BCVA ($P = 0.06$).

The DRCR.net study identified no difference between 1.25 mg and 2.5 mg of bevacizumab, and similar outcomes have been previously reported by other colleagues in retrospectively designed studies[35,36]. One of these studies involved three initial injections monthly and a follow-up period of 6 mo[33]; another study followed the same design but with a 12-mo follow-up[34]. Both studies demonstrated significant reductions in central foveal thickness (CFT) by OCT evaluation and also significant improvements in BCVA[33,34]. There were statistically similar outcomes for the two study groups throughout the 6 initial months and a trend toward recurrence of edema at the 1-year follow-up, suggesting a trend of reducing the CFT during the 2-3 mo following the intravitreal bevacizumab injection (IVBI)[33].

Another study focused on IVB for DME investigated a remarkably diverse group of eyes, with no exclusions based on previous treatment, ischemia, or poor initial BCVA[37]. The study consisted of a noncomparative trial of 1.25 mg of bevacizumab at baseline, with subsequent re-treatment based on improvement in OCT or BCVA response to the initial injection. At 6 mo, there was no significant improvement in mean BCVA, but there were significant decreases in the mean CFT according to OCT evaluation. Although some characteristics of this study led to difficulty in analyzing its results, such as the diverse baseline data and a variable number of treatments, the results corroborated the idea that bevacizumab should be the object of further studies for eyes with DME refractory to previous treatments, as this therapeutic approach was able to decrease the CFT as measured by OCT.

When investigating the long-term effects of intravitreal bevacizumab in patients with chronic diffuse DME, Kook *et al*[38] observed a decrease in central macular thickness (CMT) and again in BCVA following repeated intravitreal injections of bevacizumab, even in cases with chronicdiffuse ischemic DME.

Bonini-Filho *et al*[39] performed a pilot study of IVB-treatment for macular edema in ten eyes with severecapillary loss. The treatment used 1.5-mg dosing, and all ten eyes underwent an injection at baseline. Re-treatment at follow-up visits was based on the presence of intraretinal or subretinal fluid on OCT. After 54 wk, the CMT and BCVA improved significantly. No progression of capillary loss was observed in fluorescein angiogram at the end of the study.

The BOLT Study, a prospective, randomized, blinded, single-center study, compared IVB and macular laser photocoagulation in patients with persistent CSME after at least one macular laser treatment[40]. Eighty eyes were randomized into a bevacizumab treatment group (with injections every 6 wk), with a minimum of 3 and a maximum of 9 injections, or a photocoagulation group, with sessions every 4 mo and a minimum of 1 and a maximum of 4 treatments. After 1 year, the mean BCVA measured by ETDRS evaluation increased in the bevacizumab group and deteriorated in the laser group. The CMT results were also favorable for the bevacizumab group. The median number of injections in this first year was 9 in the bevacizumab group, and the median number of laser treatments was 3.

The 2-year outcome report of the BOLT Study was published recently and presented similar results to the first year report[41]. The mean ETDRS equivalent Snellen was 20/50 in the bevacizumab group and 20/80 in the laser group ($P = 0.005$). The bevacizumab group gained a median of 9 ETDRS letters *vs* 2.5 letters for the laser treatment group ($P = 0.005$), with a mean gain of 8.6 letters for bevacizumab *vs* a mean gain of 0.5 letters for the laser group. Among the eyes treated with bevacizumab, 32% gained at least 15 letters *vs* 4% for the laser-treated eyes ($P = 0.004$). The percentage of patient eyes that lost fewer than 15 letters in the macular laser treatment group was 86% *vs* 100% for the bevacizumab group ($P = 0.03$). At 2 years, the CMT decreased significantly in both groups. At the 2-year follow-up, the median number of injections was 13, and the median number of laser treatments was 4.

In addition to MPC,some of the largest trials published examining bevacizumab use for DME have compared intravitreal bevacizumab and intravitreal triamcinolone (IVT).

Ahmadieh *et al*[30] conducted a 24-wk trial randomizing 115 eyes to one of three study arms: a bevacizumab-only arm, an IVTA/bevacizumab combination arm, and a placebo arm. The two treatment arms received three 1.25-mg bevacizumab injections every 6 wk, and the IVTA/bevacizumab group received an additional injection of 2 mg of triamcinolone at the baseline visit only. No difference in BCVA or CMT was detected between the bevacizumab and IVTA/bevacizumab groups.

In a study performed by Faghihi *et al*[42], IVB-only was compared with bevacizumab associated to triancinolone and with MPC in eyes with no history of treatment.

Dosings of 1.25 mg of bevacizumab and 2 mg of triamcinolone were used, and injections were performed at the baseline visit only. The three groups had significant improvements in CMT at both the 6- and 16-wk visits *vs* baseline. A similar trend was observed for BCVA; the bevacizumab group outperformed the laser group in CMT and BCVA at 6 wk but not at 16 wk. The bevacizumab/IVTA group outperformed the laser group in CMT and-BCVA at both 6 and 16 wk.

A randomized clinical trial comparing IVB injection alone or in combination with IVTA *vs* macular laser photocoagulation as a primary treatment for DME was conducted by Soheilian *et al*[5,43], and the 2-year outcomes results were recently published. In total, 150 eyes were randomly assigned to 1 of the 3 study arms: the 1.25-mg IVB group; the IVB/IVT group, with 1.25 mg of IVB and 2 mg of IVT; and the macular laser group. There was significant superiority of visual acuity improvement in the IVB group after 6 mo, but this was not sustained after 24 mo. The mean BCVA improvement was greater in the IVB group than in the other groups and also in the IVB/IVT group compared with the laser group. The same was noted for the reduction of CMT, which was more evident in the IVB group compared to the other groups. However, the difference among the groups was not significant, which may be related to some methodological aspects, such as the 3-mo re-treatment intervals, when indicated, or the missing data in 24.6% of the cases at the final follow-up.

In a retrospective study, Wu *et al*[44] aimed to identify OCT patterns in diabetic DME that were predictive of visual outcomes after IVBIs. Thirty-one eyes with clinically significant DME[13] and without previous treatment underwent complete ophthalmic examination and OCT. The eyes were classified into 4 groups, based on the cross-sectional retinal morphologies, by using OCT features: diffuse retinal thickening, cystoid macular edema (CME), serous retinal detachment and vitreomacular interface abnormalities. The minimum required follow-up was 3 mo. Changes in CMT and total macular volume after IVB injections were evaluated as well as the BCVA. Patients with CME exhibited greater improvement in all evaluated parameters compared with other groups. The study concluded that OCT patterns in DME may be helpful in deciding the best treatment and predicting the outcome after IVBI. In addition, the study indicates that IVBI could be a primary therapeutic modality for CME[44]. Similar results were found in a retrospective study conducted by Roh *et al*[32].

The Pan-American Collaborative Retina Study Group has published the 24-mo results of a study examining intravitreal bevacizumab as the primary treatment for diffuse DME (DDME). For these retrospective, multicenter, interventional, comparative case series, the clinical data of 139 eyes with DDME at 11 centers from 8 countries were reviewed. All of the eyes were treated with off-label IVB with at least 1 intravitreal injection of 1.25 or 2.5 mg of bevacizumab. The dose received at baseline was the same dose delivered throughout the study. The exclusion criteria were as follows: patients with DDME that were treated with laser photocoagulation or intravitreal triamcinolone previously, macular ischemia, intraocular inflammation, a prior history of vitreoretinal surgery or cataract surgery within the past 6 mo, uncontrolled intraocular pressure, and the presence of an epiretinal membrane or vitreomacular traction syndrome. Each patient underwent BCVA measurement with ETDRS charts, ophthalmic examination and OCT at baseline and 1, 3, 6, 12 and 24 mo after the initial injection. Fluorescein angiography was performed at the discretion of the examiner (usually every 6 mo). Patients received re-injections whenever there was a recurrence of DDME.

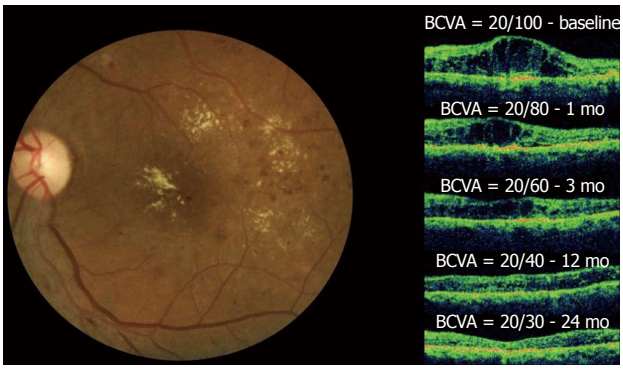

Figure 5 Diffuse diabetic macular edema treated with bevacizumab. In the left figure, the clinical fundus photograph shows the macular edema and hard exudates at the foveal center.In the right figure, a series of optical coherence tomographys (OCTs) taken at a 24-mo follow-up can be observed. The OCT image at baseline shows the intraretinal fluid with increased central macular thickness (CMT) and best-corrected visual acuity (BCVA) = 20/100. One month after the first injection, improvement in both BCVA and CMT was observed. This result was maintained throughout the 24-mo follow-up period after six injections and with final central macular thickness within normal limits without intraretinal fluid and the improvement of BCVA to 20/30. No laser photocoagulation was performed in this case.

One month after the initial bevacizumab injection, improvements in the BCVA and CMT measurements were observed, and these significant changes continued during the 24-mo follow-up period. The improvement of the BCVA and OCT from one study after 6 injections during the 2-year period is shown (Figure 5). BCVA analysis demonstrated that after 24 mo, 72 (51.8%) eyes improved 2 or more ETDRS lines, 62 (44.6%) eyes remained stable, and 5 (3.6%) eyes decreased 2 or more ETDRS lines of BCVA. A twenty-four-month OCT analysis indicated that CMT measurements decreased from 446.4 ± 154.4 μm to 279.7 ± 80 μm. The mean number of IVB injections per eye was 5.8 (range, 1-15 injections) at a mean interval of 12.2 ± 10.4 wk. The data analysis of BCVA and CMT found no significant differences between the 1.25- and 2.5-mg dose groups[45].

A systematic review of IVBI for the treatment of primary DME was conducted by Yilmaz *et al*[34] and published in 2011. The review compared IVB injection *vs* MPC *vs* a combination IVB/IVTA injection in improving the BCVA of patients without previous treatment for

DME[34]. The review included four randomized clinical trials comparing IVB injection with macular laser and three of them also comparing IVB injection with IVB/IVTA. The outcomes indicated that IVB injection is effective in improving BCVA in primary DME for 6 wk, but the benefits are no longer present at 12 wk after injection. IVTA had no detectable adjunctive effect.

Throughout the discussion of this systematic review, various limitations may be responsible for these observed outcomes, which somewhat contradict the trends shown in previous studies. First, this review was limited to four randomized controlled trials, and all of them had varied baseline characteristics. The DRCR.net study provided BCVA and CMT values that were not estimable in our analysis because there was a mixture of patients with and without prior treatment for DME. However, that study was included in the systematic review to emphasize that patients from IVB groups did improve in their BCVA and CMT values compared to the laser group. Another relevant aspect is that a decrease in efficiency may be related to the cessation of treatment in those studies in which just one injection was performed. The DRCR.net demonstrated that the improvement results were sustained for 12 wk with two IVB injections.

Therefore, the limitations of this analysis may corroborate the idea that IVB is effective in treating primary DME; however, IVB should not be considered the first line of treatment.

The safety of the intravitreal use of bevacizumab has also been studied. A retrospective study involving 1173 patients who received intravitreal bevacizumab and were followed for 12 mo is likely the largest series regarding the use of bevacizumab in DME. In this study, the following adverse effects were observed: seven cases of acute elevation of blood pressure, six strokes, five myocardial infarctions, five deaths, seven cases of bacterial endophthalmitis, seven cases of tractional retinal detachment (TRD), and four cases of uveitis[46]. These numbers were similar to those found in the prospective, controlled studies of the other anti-VEGF agents[3].

TRD in proliferative diabetic retinopathy following intravitreal bevacizumab may happen because of natural history or rapid neovascular involution with accelerated fibrosis and posterior hyaloidal contraction as a response to decreased levels of VEGF. Arevalo *et al*[47], in a retrospective review, identified a 5.2% incidence of development or progression of TRD after treatment with intravitreal bevacizumab. Therefore, treatment with bevacizumab for patients with proliferative DR and DME must be cautiously applied, especially in cases with elevated glycosylated hemoglobin, patients with type 1 diabetes with poor glycemic control, patients without previous PRP or refractory to this treatment and the presence of areas of isolated TRD.

Although delivered intravitreously, anti-VEGF drugs can potentially circulate systemically[19]. Systemic side-effects such as arterial thromboembolism, gastrointestinal perforation, hemorrhage, hypertensive crisis, and nephrotic syndrome are the main safety concerns surrounding the use of intravenous bevacizumab in patients with a diagnosis of colorectal cancer and other important systemic comorbidities.

CONCLUSION

There is growing evidence that IVBI is safe and effective for the treatment of DME, both for cases with no prior treatment as well as for refractory eyes. The rationale of the current trend of using a combination therapy of IVBI with laser photocoagulation is based on the fast recovery of macular anatomy/BCVA related to prompt VEGF inhibition (due to the IVBI) associated with the long-term effects of laser (that may decrease the necessity of IVBI due to the sustained anti-VEGF effects of laser scars).

Comparing the effects of bevacizumab and other VEGF inhibitors is difficult; however, the cost-effectiveness and safety of IVBI is certainly the most important benefit of such treatment in comparison to all commercially available anti-VEGF therapies.

To optimize the management of DME, more studies should be performed to confirm its effectiveness and the duration of its benefits and to establish guidelines for the mean number and periodicity of IVBIs, either in isolation or combined with laser photocoagulation.

ACKNOWLEDGMENTS

We would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo and Conselho Nacional de Pesquisa.

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P- Reviewer Simo R **S- Editor** Wen LL **L- Editor** A
E- Editor Li JY

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
wjd@wjgnet.com
doi:10.4239/wjd.v4.i2.27

World J Diabetes 2013 April 15; 4(2): 27-30
ISSN 1948-9358 (online)

Diabetes and renal tubular cell apoptosis

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Received: January 10, 2012 Revised: March 26, 2013
Accepted: March 28, 2013
Published online: April 15, 2013

Abstract

Apoptosis contributes to the development of diabetic nephropathy, but the mechanism by which high glucose induces apoptosis is not fully understood. Apoptosis of tubular epithelial cells is a major feature of diabetic kidney disease, and hyperglycemia triggers the generation of free radicals and oxidant stress in tubular cells. Hyperglycemia and high glucose *in vitro* also lead to apoptosis, a form of programmed cell death. High glucose similar to those seen with hyperglycemia in people with diabetes mellitus, lead to accelerated apoptosis, a form of programmed cell death characterized by cell shrinkage, chromatin condensation and DNA fragmentation, in variety of cell types, including renal proximal tubular epithelial cells.

Key words: Tubular cells; Renal; Apoptosis; Diabetes

Core tip: Apoptosis contributes to the development of diabetic nephropathy, but the mechanism by which high glucose induces apoptosis is not fully understood. High glucose similar to those seen with hyperglycemia in people with diabetes mellitus, lead to accelerated apoptosis, a form of programmed cell death characterized by cell shrinkage, chromatin condensation and DNA fragmentation, in variety of cell types, including renal proximal tubular epithelial cells.

Habib SL. Diabetes and renal tubular cell apoptosis. *World J Diabetes* 2013; 4(2): 27-30 Available from: URL: http://www.wjgnet.com/1948-9358/full/v4/i2/27.htm DOI: http://dx.doi.org/10.4239/wjd.v4.i2.27

DIABETES AND RENAL TUBULAR CELL APOPTOSIS

Diabetes is the leading cause of end-stage renal failure in most developed countries. Although vascular and glomerular injuries have been considered the main features of diabetic kidney diseases, tubular atrophy is also plays a major role in the disease[1]. Diabetes induces early signs of tubular dysfunction[2]. In addition, diabetic kidneys are particularly prone to acute tubular necrosis in diverse clinical situations, such as post-cardiac surgery[3]. Hyperglycemia, by itself, is an independent risk factor for acute tubular necrosis under these conditions[3]. Hyperglycemia triggers the generation of free radicals and oxidant stress in tubular cells[4,5]. Reactive oxygen species are considered to be important mediators for several biologic responses, including proliferation, extracellular matrix deposition and apoptosis[6]. Apoptosis, a form of programmed cell death characterized by cell shrinkage, chromatin condensation and DNA fragmentation, which, can be induced by various stimuli[7]. High glucose concentration promotes apoptosis in variety of cell types including proximal tubular epithelial cells[5,8]. The mechanism by which hyperglycemia leads to apoptosis is not completely understood.

A high glucose concentration of 30 mmol/L for 18-48 h has been shown to induce apoptotic changes in HK2 cells via an increase in oxidative stress[8]. Prolonged exposure (1-13 d) of proximal tubular epithelial cells to hyperglycemic environment has been shown to inhibit cell proliferation and induce growth arrest or cellular

apoptosis[8-12]. These cellular effects are caused by the activation of a network of intracellular signaling pathways and include the phosphatidylinostiol 3 kinase (PI3 kinase)/adams kara taylor (AKT) signaling pathway[13]. Activation of PI3 kinase and phosphorylation of serine/threonine kinase AKT/protein kinase B (PKB) by insulin, insulin like growth factors in human embryonic 293 (HEK-293) and HeLa cells lead to inactivation of tuberin by phosphorylating at Ser939, Ser1086/1088 and Thr1422[14,15]. In addition, phosphorylation of tuberin at Ser939 and Thr1422 in response to PDGF and insulin stimulation in a PI3K-dependent manner has been reported in NIH-3T3 and HEK-293 transfected with flag-tuberin[16]. Moreover, high glucose has shown to phosphorylate tuberin in renal cells[13].

Tuberin, which is the product of tumor suppressor gene, *TSC-2*[17] normally, exists in an active state physically bound to hamartin, the product of *TSC-1* gene to form a stable complex[18]. These two proteins function within the same mTOR signaling pathway. mTOR is a serine/threonine kinase involved in numerous cell processes linked to cell growth control, like cell cycle progression, transcription and translation control as well as nutrient uptake[19]. Loss of *TSC-2* function either by *TSC-2* or *TSC-1* deficiency leads to constitutive activation of mTOR and downstream signaling pathways due to increased levels of GTP-bound Rheb[20-23]. Therefore tuberin, through its Rheb-GAP activity, is a critical negative regulator of mTOR under physiological conditions[24,25]. mTOR phosphorylates p70S6K (p70 ribosomal protein S6 kinase) on Thr389, which correlates with the activation of p70S6kinase[24-26], while over-expression of TSC-2 suppresses phosphorylation and activation of p70S6K on residue Thr389[14-16]. In addition, several studies have shown that Akt/mTOR pathway is activated in diabetes and this activation is redox dependent in different cell types[27-29] including renal cells[13].

Previous reports have shown that the serine/threonine kinase, mTOR to be involved in the phosphorylation/inactivation of Bcl-2 in microtubules treated with apoptotic agents[30]. Bcl-2 plays a central role in monitoring the genetic programs of the organism[31,32]. Bcl2 related proteins comprise a family of positive and negative regulators of apoptosis. Bcl-2 and its close homolog Bcl-XL are anti-apoptotic, whereas other members of the Bcl-2 family, such as BAD or BAX are proapoptotic[33]. Bcl-2 has been shown to prevent the release of cytochrmoe C from mitochondria and hence activation of caspase 9, the initiator caspase[32]. Several kinases like JNK, p38[33] and cdc2/cyclin B kinase[34] have been noticed to phosphorylate/inactivate Bcl-2 as a physiological process during normal cell cycle progression or as a defense mechanism following the activation by various stimuli and stress. Phosphorylation/inactivation of Bcl-2 inactivates the antiapoptotic effect, which triggers the release of cytochrome C from the mitochondria leading to the activation of downstream caspases[35-37].

Another important protein involved in apoptosis is

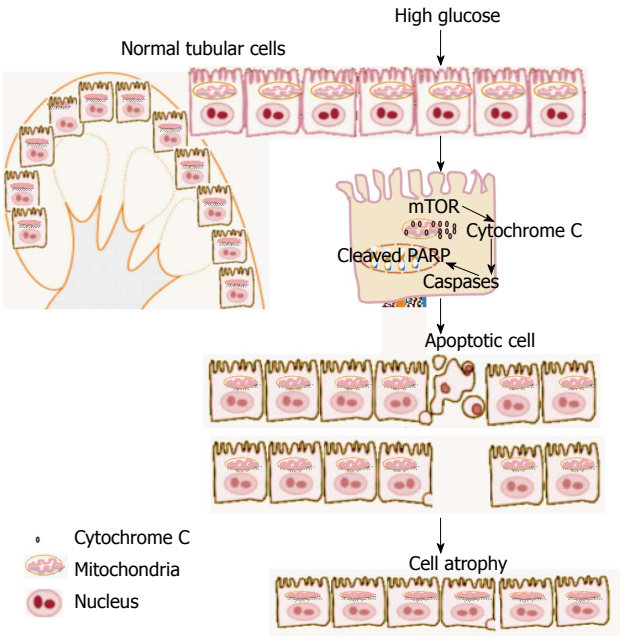

Figure 1 Proposed model of induction of cell apoptosis and subsequent of cell atrophy by high glucose in kidney.

poly (ADP-Ribose) polymerase (PARP), a DNA repair enzyme that is cleaved by the downstream caspases. The essential role of PARP activation in diabetes induced by streptozotocin in adult male BALB/c mice[38]. PARP catalyzes the poly(ADP-ribosyl)ation of a variety of nuclear proteins with NAD substrate. Because it is activated by binding to DNA ends or strand breaks, an important feature of the cell in apoptosis, PARP was suggested to contribute to apoptosis by depleting the cell of NAD and ATP[39]. When PARP is cleaved into 89- and 24-kDa fragments that contain the active site and the DNA binding domain of the enzyme, respectively during drug induced apoptosis in a variety of cells[39]. Such cleavage essentially inactivates the enzyme by destroying its ability to respond to DNA strand breaks/fragmentation.

Proteases play a critical role in the initiation and execution of apoptosis. The caspases, a family of cysteine-dependent, aspartate-directed proteases, are prominent among apoptosis-associated molecules[40]. Activation of caspases cleaves a variety of intracellular polypeptides, including major structural elements of the cytoplasm and nucleus, components of DNA repair machinery and a number of protein kinases. Caspase 3, a member of the caspase family plays a central role in the execution of the apoptotic program[41-43]. Oxidative stress mediated activation of caspase 3 has been shown to be a principle mediator of hyperglycemia induced proximal tubular apoptosis[5]. Caspase 3 is primarily responsible for the cleavage of PARP during cell death[41-45]. Recent published data show that high glucose and hyperglycemia induced cell apoptosis mainly in proximal tubular cells through regulation Bcl2/caspase/PARP pathway[46-49]. The sequence at which caspase 3 cleave PARP is very well conserved in the PARP protein from very distant species, indicating

the potential importance of PARP cleavage in apoptosis. Recent study from our lab showed the important role of tuberin/mTOR pathway in regulation of apoptosis[50]. We showed that induction of diabetes increased phosphorylation of tuberin in association with mTOR activation (measured by p70S6K phosphorylation), inactivation of Bcl-2, increased cytosolic cytochrome c expression, activation of caspase 3, and cleavage of PARP; insulin treatment prevented these changes. In addition, exposure of proximal tubular epithelial cells to high glucose increased phosphorylation of tuberin and p70S6K, phosphorylation of Bcl-2, expression of cytosolic cytochrome c, and caspase 3 activity. Moreover, high glucose induced translocation of the caspase substrate YY1 from the cytoplasm to the nucleus and enhanced cleavage of PARP. Cells treated with the mTOR inhibitor rapamycin resulted in reduce the number of apoptotic cells induced by high glucose[50]. This signaling cascade may play an important role in apoptosis induced by hyperglycemia during diabetic nephropathy. In summary, tubular apoptosis is one of the characteristic morphologic changes in human diabetic kidneys and tubular atrophy appears to be a better indicator of disease progression than glomerular pathology. A proposed model of induction of cell apoptosis and subsequent of cell atrophy by high glucose in kidney show in Figure 1. The mechanism by which hyperglycemia regulates apoptosis in renal tubular cells requires further study to provide the optimal management for diabetic complications.

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P- Reviewers Li CJ, Pacifico L **S- Editor** Huang XZ
L- Editor A **E- Editor** Li JY

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
wjd@wjgnet.com
doi:10.4239/wjd.v4.i2.31

World J Diabetes 2013 April 15; 4(2): 31-39
ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Negative association between trunk fat, insulin resistance and skeleton in obese women

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Received: December 13, 2012 Revised: February 14, 2013
Accepted: March 15, 2013
Published online: April 15, 2013

Abstract

AIM: To evaluate the potential interference of trunk fat (TF) mass on metabolic and skeletal metabolism.

METHODS: In this cross-sectional study, 340 obese women (mean age: 44.8 ± 14 years; body mass index: 36.0 ± 5.9 kg/m^2) were included. Patients were evaluated for serum vitamin D, osteocalcin (OSCA), inflammatory markers, lipids, glucose and insulin (homeostasis model assessment of insulin resistance, HOMA-IR) levels, and hormones profile. Moreover, all patients underwent measurements of bone mineral density (BMD; at lumbar and hip site) and body composition (lean mass, total and trunk fat mass) by dual-energy X-ray absorptiometry.

RESULTS: Data showed that: (1) high TF mass was inversely correlated with low BMD both at lumbar (P < 0.001) and hip (P < 0.01) sites and with serum vitamin D (P < 0.0005), OSCA (P < 0.0001) and insulin-like growth factor-1 (IGF-1; P < 0.0001) levels; (2) a positive correlation was found between TF and HOMA-IR (P < 0.01), fibrinogen (P < 0.0001) and erythrocyte sedimentation rate (P < 0.0001); (3) vitamin D levels were directly correlated with IGF-1 (P < 0.0005), lumbar (P < 0.006) and hip (P < 0.01) BMD; and (4) inversely with HOMA-IR (P < 0.001) and fibrinogen (P < 0.0005). Multivariate analysis demonstrated that only vitamin D was independent of TF variable.

CONCLUSION: In obese women, TF negatively correlates with BMD independently from vitamin D levels. Reduced IGF-1 and increased inflammatory markers might be some important determinants that account for this relationship.

Key words: Obesity; Skeleton; Vitamin D; Osteocalcin; Insulin resistance; Trunk fat; Inflammation

Core tip: Recent studies have shown that high fat mass content might be a risk factor for osteoporosis and fragility fractures. We evaluated obese women for vitamin D, osteocalcin, inflammatory markers, metabolic and hormones profile, bone mineral density (BMD) and body composition by dual-energy X-ray absorptiometry. Our results show that in obese women trunk fat negatively correlates with BMD independently from vitamin D levels, likely as consequence of reduced insulin-like growth factor-1 and increased inflammatory markers.

These data indicate that obesity cannot be considered a protective factor for osteoporosis and suggest that obese postmenopausal women should be investigated for possible alterations of skeletal metabolism.

Greco EA, Francomano D, Fornari R, Marocco C, Lubrano C, Papa V, Wannenes F, Di Luigi L, Donini LM, Lenzi A, Aversa A, Migliaccio S. Negative association between trunk fat, insulin resistance and skeleton in obese women. *World J Diabetes* 2013; 4(2): 31-39 Available from: URL: http://www.wjgnet.com/1948-9358/full/v4/i2/31.htm DOI: http://dx.doi.org/10.4239/wjd.v4.i2.31

INTRODUCTION

Obesity and osteoporosis are two important global health problems with an increasing prevalence and high impact on both mortality and morbidity[1-4]. Interestingly, during the last decades both diseases have become a major health threat around the world, with age and female status increasing the risk of developing both obesity and osteoporosis[1-4].

Obesity has been considered a protection factor against the development of bone loss and osteoporosis, likely for increased androgen aromatization to estrogens in postmenopausal obese women[5,6]. Additionally, mechanical loading appears to stimulate bone formation by decreasing apoptosis and increasing proliferation and differentiation of both osteoblasts and osteocytes[7] by an activation of the intracellular signalling Wnt/β-catenin[8-10]. Therefore, the mechanical loading conferred by body weight justified the assumption of a protective role of obesity in the prevention of osteoporosis[5].

More recently, however, the belief that obesity is protective against osteoporosis has been questioned. In fact, epidemiologic and clinical studies have suggested that high level of fat mass might be a risk factor for osteoporosis and fragility fractures[11-13]. Indeed, adipose tissue not only stores excess triacylglycerols, but functions as an endocrine organ by releasing several adipokines, which appear to modulate glucose and lipid metabolism, inflammation, appetite and insulin resistance[14-16]. Additionally, the physiological relevance of adipose tissue for skeletal health likely resides in the role that some of these adipokines, such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), might play by interfering with bone cells homeostasis[17-20]. Moreover, bone has started to be considered an endocrine organ itself affecting both body weight control and glucose homeostasis through the action of bone-derived factors such as osteocalcin and osteopontin[21,22]. This cross-talk between fat and bone seems to play an important role as homeostatic feedback system in which adipokines and molecules secreted by bone cells might represent the link of an active and functional bone-adipose-glucoseaxis[23-25], by mechanism(s) not fully clarified yet.

Recent evidences suggest that obesity is also associated with a chronic low-grade inflammation as depicted by increased plasma levels of C-reactive protein (CRP), pro-inflammatory cytokines such as TNF-α, IL-6, and osteopontin[26-30]. Few reports also depict an association between obesity and circulating low levels of vitamin D[31-33]. Nevertheless to date, few and conflicting data exist about possible correlation among vitamin D, total intact osteocalcin (OSCA), inflammatory markers[32-35] and bone mineral density (BMD) in obese women.

Since our group has recently demonstrated that a subpopulation of adult obese subjects had significant skeletal alterations, and that different levels of adiposity could differently affect skeletal health[12], the aim of the present study was to evaluate potential detrimental correlations between obesity, vitamin D levels, inflammation and BMD in obese female subjects.

MATERIALS AND METHODS

Patients

In this study, 340 women [mean age: 44.8 ± 14 years; mean body mass index (BMI): 36.0 ± 5.9 kg/m^2] were selected from a cohort of patients admitted to the day hospital of Department of Experimental Medicine, Section of Medical Pathophysiology, Endocrinology and Nutrition, Policlinico Umberto I, Sapienza University of Rome, for the diagnosis and therapy of obesity.

The study received the approval of the Internal Review Board of our Institution. Exclusion criteria were chronic medical conditions or the use of medications affecting bone metabolism, hormonal and nutritional status, vitamin D supplementation, recent weight loss, and prior bariatric surgery interventions. Patients underwent complete medical history and clinical examination. Anthropometric measurements included weight and height; body weight was measured as the subjects were fasting overnight and wearing underwear. BMI was calculated as weight (kg)/height (m^2).

Biochemical analysis

Hormones, lipid profile, glucose, insulin levels, fibrinogen, CRP, calciotropic hormones were evaluated. Additionally, OSCA, the well known most abundant non-collagenicbone matrix protein, marker of bone turnover, was measured by standard methods. Measurements of glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides and fibrinogen concentrations were assessed by standard immune-enzymatic methods, while insulin and vitamin D levels were measured by radioimmunoassay. Serum parathyroid hormone was measured by a two-site immunoradiometric assay, and CRP circulating levels were measured by latex agglutination. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma insulin and glucose levels using the formula: insulin × glucose/22.5 (mU/L × mmol/L).

Table 1 Baseline demographics of the study population (mean ± SD)

Characteristics	*n* = 340
Mean age (yr)	44.8 ± 14
BMI (kg/m^2)	36 ± 5.9
Total cholesterol (mg/dL)	196 ± 41
HDL-cholesterol (mg/dL)	49 ± 11
Triglycerides (mg/dL)	120 ± 68
HOMA-IR	4.7 ± 3
SHBG (nmol/L)	42 ± 58.5
PTH (pg/mL)	45 ± 21
Leptin (nmol/L)	75 ± 30
Vitamin D	20.5 ± 9.8
17β-estradiol	70 ± 54

BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance; Vitamin D: 25-hydroxyvitamin D; PTH: Parathyroid hormone; HDL: High-density lipoprotein; SHBG: Sex hormone binding globulin.

Dual-energy-X-ray absorptiometry measurement

Body fat mass, fat-free mass (kg) and both lumbar and femoral BMD were measured by dual-energy-X-ray absorptiometry (DEXA) (Hologic 4500 RDR), with coefficient of variation of < 1% for bone density and < 1.5% for fat mass[12]. Amount of trunk fat mass was distinguished from peripheral and appendicular fat mass as a measure of abdominal adiposity. In particular, trunk fat was defined as the adipose tissue localized within the region below the chin, delineated by vertical lines within the left and right glenoid fossae bordering laterally to the ribs, and by the oblique lines that cross the femoral necks and converge below the pubic symphysis.

Statistical analysis

Results are expressed as mean ± SD and compared by means of analysis of variance for repeated measures. Pearson correlations were used to examine associations between variables, and multiple regression analyses were used to determine the influence of TF and vitamin D on the different variables. $P < 0.05$ defined differences statistically significant as described elsewhere[12]. Multivariate linear regression analysis was carried out to identify the independent relations of TF by including the parameters which were related with TF on bivariate analysis by using SPSS/4.0 (SPSS, Chicago, IL, United States) and SAS/6.4 (SAS Institute, Cary, NC, United States).

RESULTS

A total of 340 obese women were observed and clinical characteristics are shown in Table 1, which shows the presence of obesity.

Initial analysis of the obese subjects showed a positive correlation between body weight and lumbar and femoral BMD (data not shown) as previously reported in the literature[6,36]. However, further evaluation to characterize potential relationship between fat tissue distribution and skeleton alteration showed a significant inverse relationship between TF and BMD at both lumbar and femoral sites (Figure 1), suggesting a detrimental role of abdominal fat on skeletal mass.

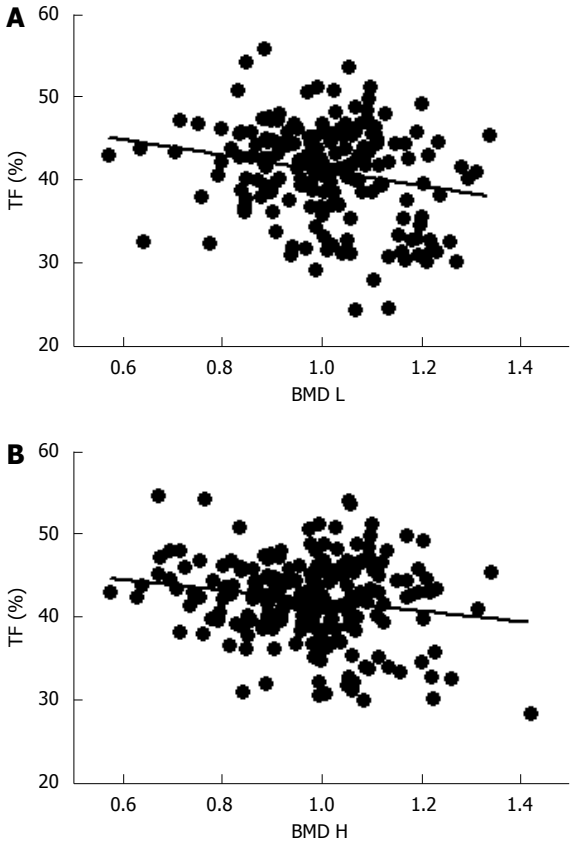

Figure 1 Correlation between trunk fat and bone mineral density at both lumbar and femoral sites. A: Trunk fat (TF) percentage and bone mineral density at the lumbar (BMD L; $r = -0.22$, $P < 0.001$); B: Bone mineral density at the hip (BMD H, $r = -0.22$, $P < 0.01$).

Further evaluation of these obese women demonstrated that vitamin D levels were significant lower than normal range, and these values were inversely correlated to either BMI (data not shown) and trunk adiposity (Figure 2A). Additionally, to correlate obesity with alteration of bone markers, OSCA levels were evaluated in these female subjects and correlated to adipose tissue. As shown in Figure 2B, OSCA levels were inversely correlated with TF mass suggesting that adipose tissue might have a detrimental effect on this specific osteoblast-specific hormone. Also insulin-like growth factor-1 (IGF-1) serum levels were inversely correlated with TF (Figure 2C). Moreover a strong direct correlation was found between vitamin D and OSCA levels (data not shown). Further, a direct relationship between TF and HOMA-IR index (Figure 3A), and inflammatory markers such as fibrinogen (Figure 3B) and erythrocyte sedimentation rate (Figure 3C) was found in these obese adult female subjects indicating, as suggested by others[21,22], a potential role of TF in glucose homeostasis. Analysis carried out to investigate possible relationship between IGF-1 levels and vitamin D status showed a strong direct relationship (Figure 4A). Also, vitamin D levels were directly corre-

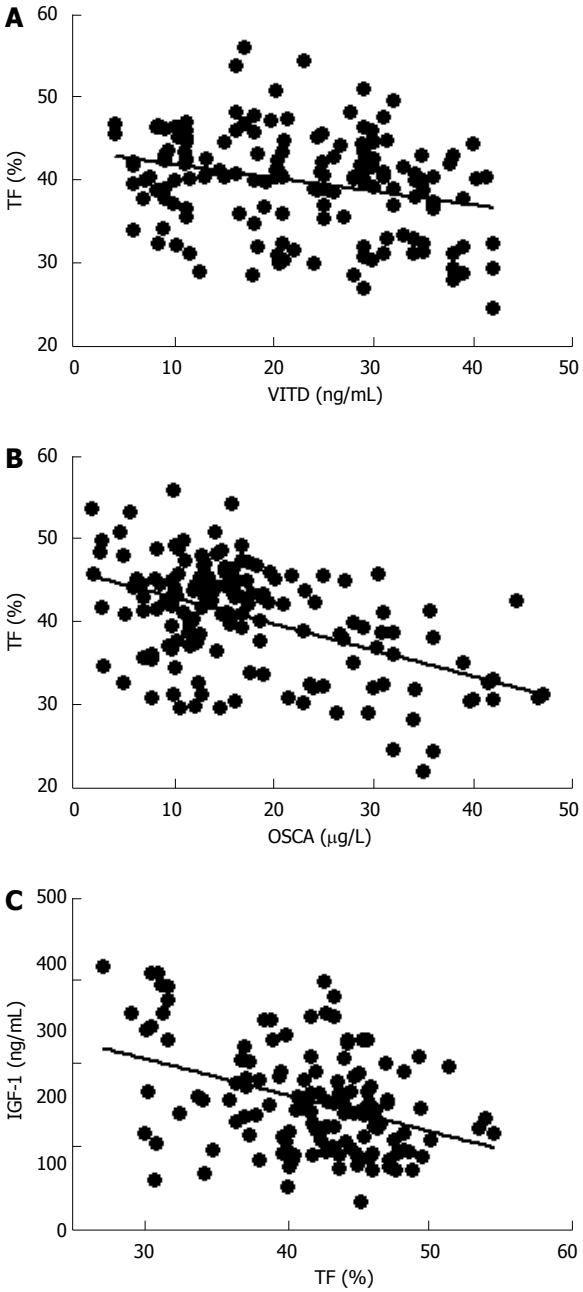

Figure 2 Inverse relationship between trunk fat percentage and vitamin D (A; $r = -0.27$, $P < 0.0005$), osteocalcin (B; $r = -0.49$, $P < 0.0001$) and insulin-like growth factor-1 (C; $r = -0.31$, $P < 0.0001$) plasma levels in obese women. VITD: Vitamin D; OSCA: Osteocalcin; IGF-1: Insulin-like growth factor-1; TF: Trunk fat.

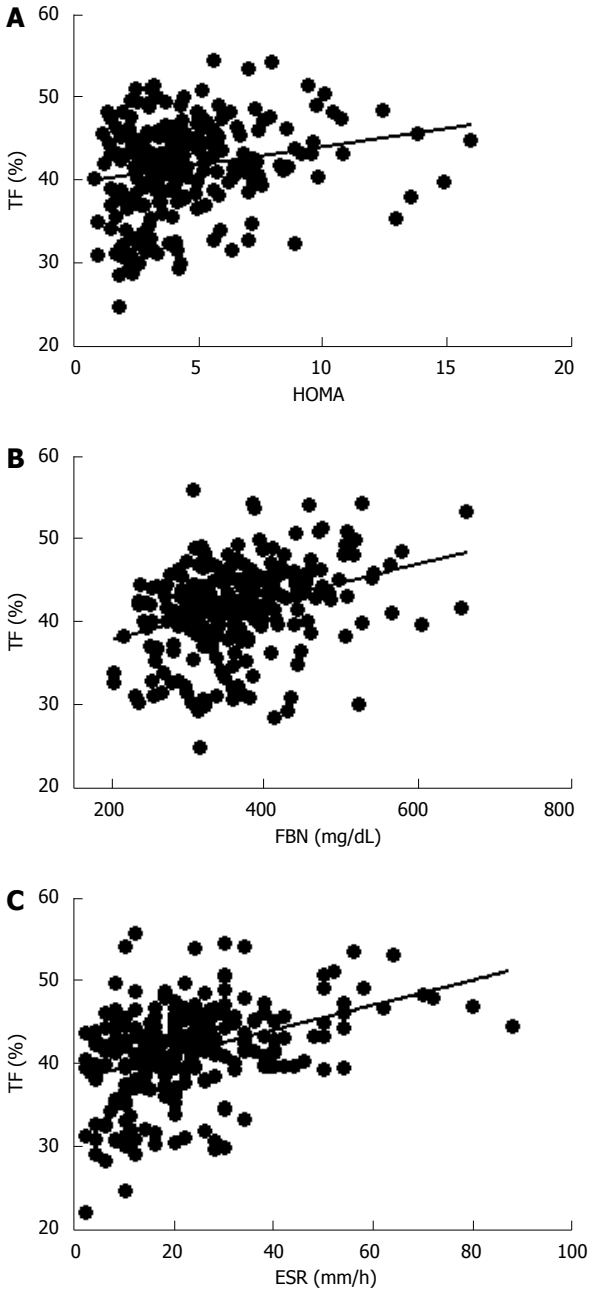

Figure 3 Direct relationship between trunk fat percentage, homeostasis model assessment index (A; $r = 0.18$, $P < 0.01$), fibrinogen (B; $r = 0.44$, $P < 0.0001$) and erythrocyte sedimentation rate (C; $r = 0.29$, $P < 0.0001$) in obese women. HOMA: Homeostasis model assessment; FBN: Fibrinogen; ESR: Erythrocyte sedimentation rate; TF: Trunk fat.

lated with BMD at the femoral (Figure 4B) and lumbar (Figure 4C) sites and inversely correlated with HOMA-IR (Figure 5A) and fibrinogen levels (Figure 5B). Since it is known that obesity is associated with a low-grade inflammation[37,38], specific markers were also investigated. As expected, inflammatory markers were significantly elevated in obese women (Table 2) with a strong correlation with degree of obesity. Multivariate analysis demonstrated that only vitamin D was the only parameter that resulted to be independent from TF (Table 3).

DISCUSSION

The results presented herein show for the first time that in obese women, the amount of TF is negatively correlated with BMD, vitamin D, osteocalcin and IGF-1 levels, whereas it is directly correlated with insulin insensitivity and inflammation markers. Also, vitamin D status was directly correlated with IGF-1 levels and multivariate analysis showed that it was the only parameter that was independently associated with TF. This represents a novel

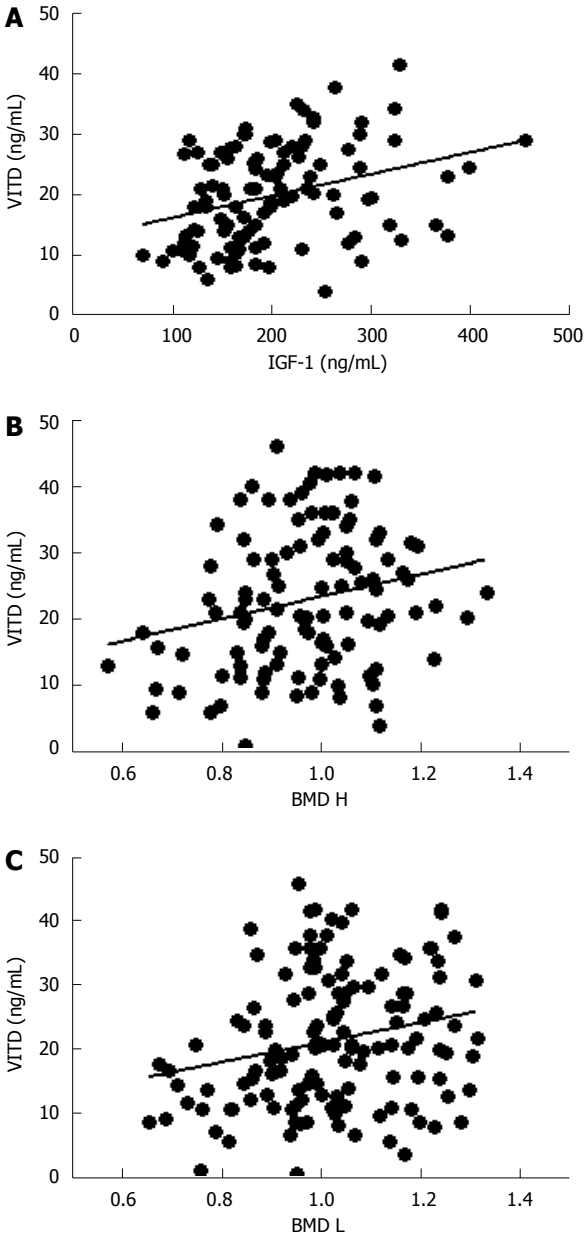

Figure 4 Direct relationship between vitamin D, insulin-like growth factor-1 (A; $r = 0.32$, $P < 0.0005$), hip (B; $r = 0.23$, $P < 0.01$) and lumbar bone mineral density (C; $r = 0.19$, $P < 0.005$) in obese women. VITD: Vitamin D; IGF-1: Insulin-like growth factor-1; BMD H: Bone mineral density at the hip; BMD L: Bone mineral density at the lumbar; TF: Trunk fat.

finding in obese women, suggesting that vitamin D and IGF-1 levels might be considered a sensitive predictor and indicator of skeletal health, as bone mineral density alteration itself.

Fat tissue is present throughout the body and, in cases of obesity, can cover up to 50% or more of the entire body mass. White adipose tissue (WAT) is the most abundant form, found in both subcutaneous and intra-abdominal regions. WAT was first regarded only as an energy reservoir, however it is now well recognized as an endocrine organ due to its secretion of circulating adipokines and pro-inflammatory factors[14-20]. Obesity, defined as an abundance of WAT, has always been depicted as a

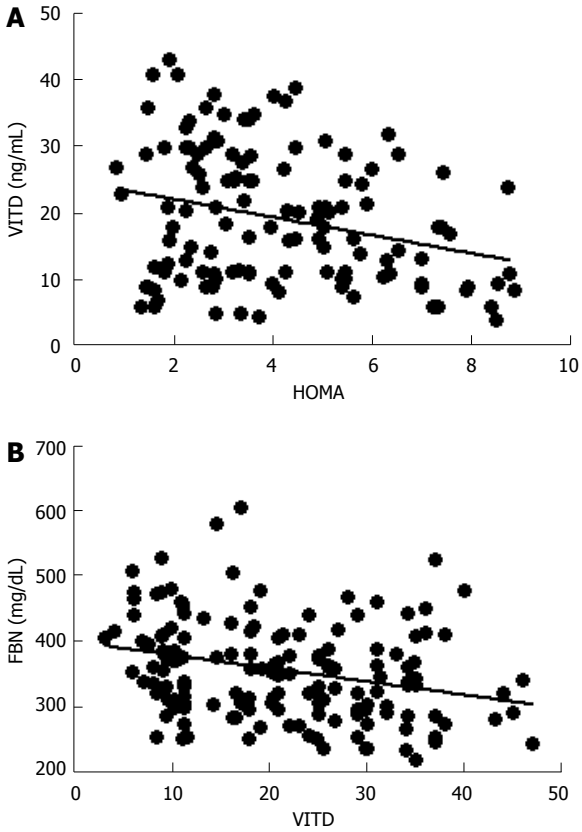

Figure 5 Inverse relationship between vitamin D levels with homeostasis model assessment (A; $r = -0.27$, $P < 0.001$) and with fibrinogen (B; $r = -0.28$, $P < 0.0005$). VITD: Vitamin D; HOMA: Homeostasis model assessment; FBN: Fibrinogen.

protective factor against the development of bone loss and osteoporosis[5,6], nevertheless several groups, including ours[11-13], have recently demonstrated that high amounts of adipose tissue accumulation might not be considered a protective factor against the development of osteoporosis and fracture risk.

Thus, the main objective of our study was to evaluate the relationship between obesity (BMI > 30 kg/m^2) and BMD modifications. Interestingly, while BMD was correlated to BMI, body weight appeared to be a protective factor against low bone mass (data not shown), as previously reported in the literature[5,6], which led to claim a protective role of obesity against bone loss and osteoporosis. However, data were re-analyzed to evaluate potential detrimental role of body fat distribution on skeletal health. This evaluation demonstrated that higher level of TF correlated with lower bone mass, strongly suggesting that BMI might not be considered the unique parameter to evaluate potential detrimental effect of fat tissue as risk factors for cardiovascular, metabolic or skeletal disorders[1-2,23,39-42]. Indeed, recent data indicate that TF might correlate with skeletal damages in young population as well[43].

Moreover, although obese subjects have greater calories intake than subjects with normal body weight, they often show nutritional deficiencies or alterations in hormonal or metabolic parameters. For instance, obese women show very low concentrations of vitamin D, as described

Table 2 Biochemical and hormonal characteristics of the study population according to different body mass index

	BMI < 30 kg/m^2 (n = 80)	BMI 30-35 kg/m^2 (n = 100)	BMI 35-40 kg/m^2 (n = 80)	BMI > 40 kg/m^2 (n = 80)
BMI	27 ± 1.2	32.5 ± 1[b]	37 ± 1.5[b]	44 ± 2[b]
Mean age (yr)	46.5 ± 15	45 ± 14	46 ± 13	43 ± 14
Total-cholesterol (mg/dL)	199 ± 54	198 ± 41	204 ± 40	190 ± 32
HDL-cholesterol (mg/dL)	52 ± 13	50 ± 11	50 ± 10	46 ± 10
Triglycerides (mg/dL)	114 ± 79	117 ± 61	130 ± 72	122 ± 68
Fibrinogen (mg/dL)	346 ± 102	341 ± 63	368 ± 85	421 ± 86[b]
C-reactive protein (ng/mL)	2 ± 0.9	2.8 ± 0.9	5.0 ± 1.4[b]	5.5 ± 2.1[b]
HOMA-IR	2.8 ± 0.9	3.1 ± 0.8	5.0 ± 2.6[b]	6.4 ± 2.2[b]
PTH (pg/mL)	40 ± 15	42 ± 20	46 ± 23	48 ± 19
Vitamin D	26 ± 9	20 ± 10[b]	16 ± 8[b]	15 ± 10[b]

[b]P < 0.01 *vs* BMI < 30 kg/m^2. BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance; Vitamin D: 25-hydroxyvitamin D; PTH: Parathyroid hormone; HDL: High-density lipoprotein.

Table 3 Multivariate analysis showing that vitamin D is the only parameter that is independently associated with trunk fat percentage

	Unstandardized coefficients[1]		Standardized coefficients[1]		
Model	B	SE	*Beta*	*t*	*P* value
1 (constant)	52.054	8.498		6.125	0.000
Lumbar BMD	6.570	8.121	0.167	0.809	0.437
Hip BMD	-9.971	7.687	-0.259	-1.029	0.224
Vitamin D	-0.359	0.077	-1.029	-4.666	0.001
Osteocalcin	0.134	0.111	0.255	1.208	0.255
IGF-1	-0.002	0.014	-0.022	-0.114	0.916

[1]Dependent variable of trunk fat. IGF-1: Insulin-like growth factor-1; BMD: Bone mineral density.

by others[33-35], as well as the osteoblast-produced OSCA, which were inversely correlated to TF mass, suggesting that alteration of biochemical and hormonal parameters might be an indicator of skeletal damage and decreased density as diagnosed by DEXA. As previously shown by others, we also observed an inverse relationship between vitamin D and BMI, likely due to the amount of adipose tissue, which, in individuals who are not obese, is inversely associated with its blood concentrations[44,45]. As described in the literature,we confirmed a positive correlation between low vitamin D circulating levels and low BMD also in obese women, but we found a new direct relationship between vitamin D, IGF-1 and TF; this highlights the fact that bone tissue might indeed play a pivotal role in the recently described feedback among fat, bone and glucose metabolism[25,46,47].

In the last years, potential association between obesity, cardiovascular and metabolic diseases such osteoporosis, has been actively investigated and common pathogenic links have been proposed since all are influenced by genetic and environmental factors, or by the interaction of such factors. Aging is associated with these chronic diseases and with a high incidence of bone loss and bone marrow adiposity; in turn, bone remodeling and adiposity are regulated through a complex concert of adipokines and hormone interactions. Indeed, adipocytes and osteoblasts derive from a common progenitor cell, that is the mesenchymal stem cell[23,48], and several potential mechanisms have been proposed to explain the complex relationship between adipose and bone tissues[47-50].

Adipose tissue was long viewed as a passive energy reservoir, but since the discovery of leptin, and other adipose tissue-derived factors[28,49,50], fat has been considered an active endocrine organ. Indeed, it (TF) secretes inflammatory cytokines, such as IL-6 and TNF-α[51], which appear to play a pivotal role in the maintenance of the low-grade inflammatory status of obesity, leading to the development of adverse metabolic and cardiovascular consequences and, likely, contributing to the detrimental effect of fat tissue on the skeleton[20].

Evidences suggest that an inflammatory status might be involved in the pathogenesis of osteoporosis promoting osteoclasts differentiation and activity and maintaining an altered bone remodeling[52-57]. Recently, CRP, an inflammatory marker, has been identified as an independent risk factor for cardiovascular events in healthy postmenopausal women[52-57] and high serum levels of CRP are also associated with lower BMD, higher levels of bone turnover markers and, more recently, greater risk of fracture[52-57], further suggesting a role of inflammation in bone loss pathogenesis. At the present time it is unknown whether CRP plays a pivotal role as mediator of bone loss similarly to its role in atherosclerosis[57] or whether is only a marker of systemic inflammation, linked to bone health alterations[53]. In the present study we found an association between inflammatory markers, *i.e.,* of erythrocyte sedimentation rate and fibrinogen, vitamin D levels and insulin resistance, thus suggesting that a higher degree of inflammation might be in part responsible for deterioration of bone health.

Finally, we also found a negative correlation between high degree of obesity and IGF-1 level (inversely related to lean mass, data not shown) which also correlated with lower BMD in obese women. The importance of this factor in bone tissue homeostasis is well known[57] both during infancy and adulthood, but our data further in-

dicate that a complex metabolic and hormonal pattern alteration exist in obesity which is linked to bone homeostasis alteration.

In conclusion, our data show that TF plays a detrimental role in skeletal metabolism both in term of low BMD, bone markers and systemic factors influencing skeletal tissue. Finally, alteration of vitamin D levels, and inflammation status, in association with low OSCA, altered insulin sensitivity might indicate the existence of an important interplay between bone tissue, energy metabolism and inflammations, which might suggest a common pathogenic mechanism in the development of metabolic, cardiovascular and skeletal diseases. Further studies are however needed to fully clarify and characterize the mechanism(s) underlying the role of trunk fat in the development effect of chronic diseases, such diabetes, cardiovascular disease and osteoporosis.

COMMENTS

Background

Obesity and osteoporosis are two important global health problems with an increasing prevalence and high impact on both mortality and morbidity. The belief that obesity is protective against osteoporosis has been questioned. In fact, epidemiologic and clinical studies have suggested that high level of fat mass might be a risk factor for osteoporosis and fragility fractures

Research frontiers

Recent evidences suggest that obesity is also associated with a chronic low-grade inflammation as depicted by increased plasma levels of C-reactive protein, pro-inflammatory cytokines. Few reports also depict an association between obesity and circulating low levels of vitamin D.

Innovations and breakthroughs

The results presented herein show for the first time that in obese women, the amount of trunk fat (TF) is negatively correlated with bone mineral density (BMD), vitamin D, osteocalcin and insulin-like growth factor-1 (IGF-1) levels, whereas it is directly correlated with insulin insensitivity and inflammation markers.

Applications

This data show that TF plays a detrimental role in skeletal metabolism both in term of low BMD, bone markers and systemic factors influencing skeletal tissue.

Peer review

This is an interesting article on the associations of trunk fat with inflammation biomarkers, IGF-1 and bone density in severe obese women.

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P- Reviewers Andrei S, Kanda T **S- Editor** Zhai HH
L- Editor A **E- Editor** Li JY

World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
wjd@wjgnet.com
doi:10.4239/wjd.v4.i2.40

World J Diabetes 2013 April 15; 4(2): 40-46
ISSN 1948-9358 (online)

BRIEF ARTICLE

Parental transmission of type 2 diabetes mellitus in a highly endogamous population

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Supported by Qatar Diabetic Association and Qatar National Research Fund, QNRF UREP 07-099-3-023
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Received: December 5, 2012 Revised: March 6, 2013
Accepted: March 15, 2013
Published online: April 15, 2013

Abstract

AIM: To determine the parental transmission of diabetes mellitus (DM) and evaluate its influence on the clinical characteristics.

METHODS: This was a cross sectional study. The survey was carried out in urban and semi-urban primary health care centers. Of the 2400 registered with diagnosed diabetes, 1980 agreed and gave their consent to take part in this study, thus giving a response rate of 82.5%. Face to face interviews were conducted using a structured questionnaire followed by laboratory tests. DM was defined according to the World Health Organization expert group. A trained nurse performed physical examinations and measurements.

RESULTS: Of the study population, 72.9% reported a family history of DM. Family history of DM was significantly higher in females (54.2%; $P = 0.04$) and in the age group below 30 years (24%; $P < 0.001$). The prevalence of diabetes was higher among patients with a diabetic mother (25.4% *vs* 22.1%) and maternal aunts/uncles (31.2% *vs* 22.2%) compared to patients with a diabetic father and paternal aunts/uncles. Family history of DM was higher in patients of consanguineous parents (38.5%) than those of non-consanguineous parents (30.2%). The development of type 2 diabetes mellitus (T2DM) complications was higher in patients with either a paternal or maternal history of DM than in those without. No significant difference was observed in the metabolic characteristics of patients with/without family history of DM except for hypertension. Complications were higher in diabetic patients with a family history of DM.

CONCLUSION: The present study found a significant maternal effect in transmission of T2DM. Family history is associated with the increased incidence of diabetes.

Key words: Diabetes mellitus; Family history; Parental transmission; Genetic disorders; Consanguinity; Maternal transmission

Core tip: Diabetes is a disease that has a strong clustering in families and has a genetic component. Family history is a well-known risk factor for developing of type 2 diabetes mellitus (T2DM). The present study found a significant maternal effect in transmission of T2DM. Family history is associated with the increased incidence of diabetes.

Bener A, Yousafzai MT, Al-Hamaq AOAA, Mohammad AG, DeFronzo RA. Parental transmission of type 2 diabetes mellitus

in a highly endogamous population. *World J Diabetes* 2013; 4(2): 40-46 Available from: URL: http://www.wjgnet.com/1948-9358/full/v4/i2/40.htm DOI: http://dx.doi.org/10.4239/wjd.v4.i2.40

INTRODUCTION

Diabetes is a multifactorial disease that involves complex interactions between genes, environment and health behavior. Type 2 diabetes mellitus (T2DM) is a common metabolic disorder, characterized by hyperglycemia caused by impaired glucose homeostasis, and represents a serious public health problem in many developed countries[1]. Current studies have revealed a definite global increase in the incidence and prevalence of diabetes. In 2000, 171 million people were estimated to be diabetic worldwide, which is projected to rise to 366 million cases in the year 2030[2]. It is the fourth or fifth leading cause of death in most developed countries[1]. Given the growing rate of diabetes and its far reaching societal and economic consequences, prevention of diabetes among people at high risk is a public health issue of clinical importance.

Diabetes is a disease that has a strong clustering in families and has a genetic component. It has been widely reported that the occurrence of T2DM is triggered by a genetic susceptibility and familial aggregation in several populations[3,4]. Family history is a well-known risk factor for the developing of T2DM. It was estimated that risk for diagnosed T2DM increases approximately two to four fold when one or both parents are affected[5]. Almost 25% to 33% of all T2DM patients have family members with diabetes. Having a first degree relative with the disease poses a 40% risk of developing diabetes[6]. T2DM patients are more likely to have diabetic mothers than diabetic fathers. The existence of excess maternal transmission of T2DM in offspring of affected mothers than affected fathers is currently debated[7]. Family history reflects both inherited genetic susceptibilities and shared environments which include cultural factors[8]. Thus, family history of diabetes may be a useful tool to identify individuals at increased risk of the disease and target behavior modifications that could potentially delay disease onset and improve health outcomes.

It was reported that several genetic disorders, congenital malformations and reproductive wastage are more frequent in consanguineous marriages[9]. A previous study by Bener *et al*[10] showed significant increase in the prevalence of common adult diseases in a population with a high rate of consanguinity. The incidence of consanguinity (51%) is relatively high in the State of Qatar with first cousin marriage predominantly comprising 26.7% of all marriages.

In Qatar, it was reported that diabetes is on the rise and if proper intervention and preventive strategies were not adopted, the epidemic of diabetes will prove fatal. The upcoming epidemic and projected increase in the prevalence of diabetes over the next two decades emphasize the importance of early detection[11] of diabetes in the population. Few studies have documented the prevalence of T2DM and its complications in the population of Qatar[12,13]. To the best of our knowledge, the patterns of familial transmission of T2DM in Qatar have not been studied so far. The significance of maternal or paternal inheritance in diabetes has been a matter of controversy and difference in various populations and races. Hence, this is the first cross-sectional survey of the Arab population in Qatar to determine the influence of familial history of T2DM in the offspring and evaluate its influence on the clinical characteristics of this disease.

MATERIALS AND METHODS

This is a cross-sectional study which was conducted among diabetic patients registered in diabetic clinics of primary health care (PHC) centers of the Supreme Council of Health. The diabetes care is organized in most of the PHC centers. During the study period from January 2010 to January 2011, the study included T2DM patients registered in these diabetic clinics who were taking oral hypoglycemic drugs. In this study, multistage stratified cluster sampling was employed using the administrative divisions of the PHC in Qatar. Target population of each PHC is approximately equal. Stratification was done to obtain a representative sample of target population, with equal proportions from both urban and semi urban areas. The sample size was statistically calculated based on 17% prevalence rate of diabetes in Qatar[13], with 1% level of significance and assuming 2% bound on error of estimation, giving a minimum sample size of 2400 subjects for this study. Of the 2400 patients approached from different PHC centers (10 centers from an urban area and 2 centers from a semi-urban area), 1980 agreed to participate and gave verbal consent to take part in this study (82.5%). Also, any patients with incomplete laboratory values in the medical records were excluded from the study. The study was approved by the Hamad Medical Corporation prior to commencing data collection.

Questionnaire

We developed a structured questionnaire consisting of questions relating to socio-demographic data, family history of diabetes mellitus (DM), lab investigations and complications. The first part included information about socio-demographic characteristics, including age, sex, marital status, education level, occupation, height, weight, blood pressure and parental consanguinity. The second section collected information about family history of DM with family relations and complications after the onset of diabetes. The third section included items about laboratory investigations such as blood glucose, glycated hemoglobin, high-density lipoprotein/low-density lipoprotein cholesterol levels, triglyceride, urea, creatinine, bilirubin, albumin *etc*. Necessary corrections and modifications were made in the questionnaire after the pilot study. Content validity, face validity and reliability of the questionnaire were tested using 50 subjects. These tests demonstrated a high level of validity and high degree of repeatability (kappa = 0.84)[14]. Family physicians and research nurses reviewed the medical files of diabetic patients in PHC and recorded all lab

investigation measurements from their files.

Physical examination and other measurements

A trained nurse performed physical examinations and measurements. In order to measure height (m), participants were asked to stand in bare feet while maintaining a straight posture on a height scale (SECA, Germany). Similarly, weight (kg) was measured using the same scale with light clothing and bare feet. Body mass index was calculated as the ratio of weight (kg) to the square of height (m).

Hypertension was defined as per World Health Organization (WHO) standardized criteria, "systolic blood pressure (SBP) ⩾ 140 mmHg or diastolic blood pressure (DBP) ⩾ 90 mmHg or using anti-hypertensive medication"[15]. In order to measure blood pressure, subjects were asked to sit and rest for at least 10-15 min. Two readings of SBP and DBP were taken from his/her left arm at heart level while using standard zero mercury sphygmomanometer. An average of both readings for SBP and DBP was obtained.

Laboratory measurements

Study participants with a history of T2DM and currently taking oral anti-diabetic medications were considered to have DM. DM was defined as per the WHO expert group[16], *i.e.,* fasting venous blood glucose (FBS) concentration ⩾ 7.0 mmol/L and/or 2 h post-oral glucose tolerance test (OGTT) venous blood glucose concentration ⩾ 11.1 mmol/L. FBS was measured by glucose meter among all the participants and those with FBS < 7 mmol/L were further tested by an OGTT. In order to conduct OGTT, participants were asked to drink 75 g anhydrous glucose dissolved in 250 mL water within the space of 5 min. Samples were processed within 30 min of collection and the above laboratory tests were measured. Subjects with impaired FBS (venous blood glucose concentration for 5.6-6.9 mmol/L) or impaired OGTT (2 h post-OGTT venous blood glucose level of 7.8-11.0 mmol/L) were labeled as pre-diabetes. Glycosylated hemoglobin was analyzed using a high-performance liquid chromatography method with a range > 6.5% defined as "unsatisfactory" metabolic control.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 19) software. Standard descriptive statistical analysis was performed. Student *t* test was used to ascertain the significance of differences between mean values of two continuous variables and one way analysis of variance was used to find the differences between continuous variables among more than two groups. Differences between categorical variables were tested through Pearson χ^2 or Fisher's exact test when the assumptions for χ^2 test were not fulfilled. Two sided *P* value of less than 5% was considered as significant.

RESULTS

Table 1 shows the socio-demographic characteristics of patients with/without a family history of DM. Family history of DM was significantly higher in female patients (54.2%; $P = 0.041$), Qatari nationals (58%; $P = 0.020$) and in the age group below 30 years (24%; $P < 0.001$). Consanguinity was significantly higher in diabetic patients with family history of DM (38.5% *vs* 30.2%; $P = 0.001$) compared to those without family history of DM.

Table 1 Socio-demographic characteristics of patients with/without a family history of diabetes mellitus *n* (%)

	With family history of DM[1] (*n* = 1444)	Without family history of DM (*n* = 536)	*P* value
Age (yr)			< 0.001
18-30	346 (24.0)	72 (13.4)	
30-39	280 (19.4)	66 (12.3)	
40-49	258 (17.9)	132 (24.6)	
50-59	400 (27.7)	194 (36.2)	
⩾ 60	160 (11.1)	72 (13.4)	
Gender			0.041
Male	661 (45.8)	273 (50.9)	
Female	783 (54.2)	263 (49.1)	
Nationality			0.020
Qatari	838 (58.0)	342 (63.8)	
Other Arabs	606 (42.0)	194 (36.2)	
Educational level			0.154
Illiterate	240 (16.6)	71 (13.2)	
Elementary	267 (18.5)	114 (21.3)	
Intermediate	305 (21.1)	99 (18.5)	
Secondary	381 (26.4)	152 (28.4)	
University	251 (17.4)	100 (18.7)	
Occupation			0.134
Housewife	370 (25.6)	128 (23.9)	
Sedentary	356 (24.7)	162 (30.2)	
Professional	249 (17.2)	97 (18.1)	
Manual	153 (10.6)	53 (9.9)	
Businessmen	127 (8.8)	39 (7.3)	
Army/police clerk	189 (13.1)	57 (10.6)	
Monthly household income (QR)			0.589
< 5000	93 (6.4)	39 (7.3)	
5000-10 000	470 (32.5)	175 (32.6)	
10 000-15 000	510 (35.3)	200 (37.3)	
> 15 000	371 (25.8)	122 (22.8)	
Consanguinity			0.001
Yes	556 (38.5)	162 (30.2)	
No	888 (61.5)	374 (69.8)	

[1]Up to the third generation, two sided *P* values based on Pearson χ^2 test. DM: Diabetes mellitus; QR: Qatar Riyal.

Table 2 reveals the familial history of diabetes mellitus among diabetic patients. Of the total study population, 72.9% reported a family history of DM. The prevalence of DM in father, mother, brother and sister was 22.1%, 25.4%, 14.2% and 9.3% respectively. In 2nd degree relatives for uncles and aunts, a positive history of T2DM was more common among maternal aunts/uncles than in paternal aunts/uncles (31.2% *vs* 22.2%). On the maternal side, 83.7% of the diabetic patients have an affected mother (25.4%) and at least one relative (58.3%), compared to only 67.3% of diabetic patients with an affected father (22.1%) and one family member (45.2%) on the paternal side.

Table 3 gives physical, metabolic characteristics and complications among diabetic patients according to the

Table 2 Familial history of diabetes mellitus among diabetic patients *n* (%)

	n = 1980
Family history of diabetes[1]	
Negative	536 (27.1)
Positive	1444 (72.9)
Family relations	
Father	437 (22.1)
Mother	503 (25.4)
Brother	281 (14.2)
Sister	184 (9.3)
Paternal uncle	244 (12.3)
Paternal aunt	195 (9.8)
Maternal uncle	325 (16.4)
Maternal aunt	293 (14.8)
Paternal grand father	235 (11.9)
Paternal grand mother	221 (11.2)
Maternal grand father	264 (13.3)
Maternal grand mother	272 (13.7)

[1]Up to the third generation.

family history of DM. No significant difference was found in the metabolic characteristics of diabetic patients according to the family history of DM except for the SBP (P = 0.033) and DBP (P = 0.025). The development of T2DM complications was higher in patients with either a paternal or maternal history of DM than in those without; significantly higher for sleep loss (13.9% *vs* 6.7%, 12.2% *vs* 6.7%; P < 0.001), hypertension (29.6% *vs* 20.9%, 22% *vs* 20.9%; P = 0.001), retinopathy (17.6% *vs* 11.4%, 13.3% *vs* 11.4%; P = 0.006) and antipathy (8% *vs* 4.7%, 7.7% *vs* 4.7%; P = 0.047).

Table 4 shows physical and clinical characteristics and complications of T2DM according to family history of DM, while controlling for consanguinity. Out of 718, 556 (77.4%) of the diabetic patients of consanguineous parents had either a paternal (233/718; 32.5%) or maternal history (323/718; 45%) of DM; whereas family history of DM was lower in patients of non-consanguineous parents (888/1262; 70.4%). No significant difference was found in metabolic characteristics of patients according to the presence of DM in parents and relatives except for the SBP and DBP, found to be significantly higher among patients with maternal history of DM in the consanguineous group (P = 0.018, P = 0.007, respectively). In addition, hypertension, retinopathy and antipathy were significantly higher among patients with a paternal history of DM in the consanguineous group (P = 0.002, P = 0.007, P = 0.003, respectively). No significant difference was found in T2DM complications of patients according to paternal/paternal history of DM in the non-consanguineous group.

Figure 1 shows the association between consanguinity and family history of DM in an Arab diabetic population in Qatar. The Venn diagram clearly shows the overlapping of parental consanguinity with a paternal and maternal history of diabetes mellitus.

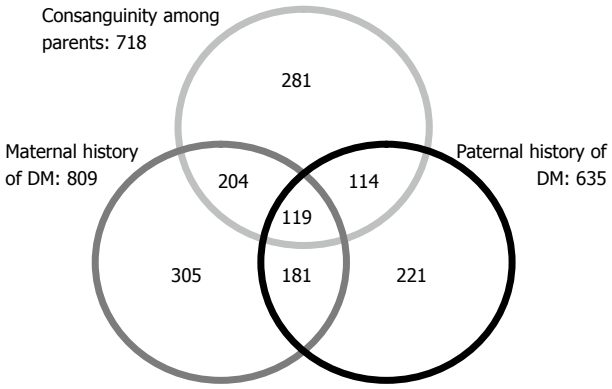

Figure 1 Association between consanguinity and family history of diabetes mellitus in an Arab diabetic population in Qatar (*n* = 1980). DM: Diabetes mellitus.

DISCUSSION

In the State of Qatar, as a result of changing lifestyle due to rapid urbanization, the prevalence of T2DM is increasing, as is observed worldwide. However, the role of genetic and environmental factors remains unclear. This is the first study to provide insight in the familial aggregation and transmission patterns of T2DM among an Arab population residing in Qatar. The study sample revealed that 72.9% of the subjects with DM had a positive family history of diabetes among at least one of their parents, siblings, uncles, aunts and grandparents. The degree of familial aggregation of diabetes among Tunisians[17] found that 70% of the diabetic patients had a positive family history of diabetes among at least one of their relatives from both sides, which is nearly identical to our study. A lower rate was observed in a French study[3] in which 66% of the diabetic patients had at least one relative with diabetes among their first and second degree relatives. Similar higher frequencies have also been reported among South Indians[18] (53.9%) and Pakistanis (70%)[19]. On the other hand, lower frequencies of positive family history have been reported by other studies in Asians[4] (36%), Europeans[20] (33%) and black South Africans (27%)[3]. In the study sample of 1980 diabetic patients, 71% reported at least one first degree familial member, which is similar to the study results of Crispim *et al*[21] (76.6%). These results support the strong familial aggregation of diabetes among an Arab population with a high prevalence among 1st degree relatives. Also, these study findings have proven that people with a family history of diabetes consider themselves to be at greater risk of developing diabetes in their offspring. These results are in agreement with a study by Hariri *et al*[22] that a family history of diabetes in a first-degree relative doubles a person's risk of developing diabetes.

Another important study finding was that the investigation of parental transmission patterns of T2DM showed an excess of maternal transmission of T2DM as mothers were implicated more frequently than fathers[23]. In the study sample, 25.4% of the mothers of the diabetic patients were diabetic compared to 22.1% of the fathers.

Table 3 Physical, metabolic characteristics and complications among diabetic patients according to family history of diabetes mellitus (*n* = 1980)

Parameters	Family history[1]		No family history of DM	*P* value
	Paternal history (*n* = 635)	Maternal history (*n* = 809)	(*n* = 536)	
Age (yr)	44.9 ± 14	45.1 ± 15	46.7 ± 13.3	0.073
Duration of diagnosis (yr)	6.9 ± 4.2	7.3 ± 4.3	6.4 ± 3.3	0.001
BMI (kg/m^2)	27.4 ± 4.9	26.8 ± 4.8	27.7 ± 4.9	0.033
Metabolic characteristics				
Systolic blood pressure (mmHg)	129.9 ± 19.5	129.1 ± 18.1	127.1 ± 14.7	0.033
Diastolic blood pressure (mmHg)	81.3 ± 11	80.4 ± 10.5	79.4 ± 8.5	0.025
Fasting glucose (mmol/L)	9.9 ± 8.0	9.1 ± 5.0	9.1 ± 4.7	0.092
HbA1c	8.2 ± 2.2	7.9 ± 2.1	8.1 ± 2.2	0.188
Serum urea level	5.9 ± 1.5	6.3 ± 2.3	5.8 ± 1.7	0.135
Serum creatinine (mmol/L)	77.2 ± 9.5	78.1 ± 9.8	73.8 ± 8.6	0.371
Total cholesterol (mmol/L)	5.0 ± 1.1	4.8 ± 1.1	4.9 ± 1.2	0.095
Serum alkaline phosphate	94.6 ± 11.3	101.7 ± 13.8	100 ± 12.4	0.402
T2DM complications, *n* (%)				
Sleep loss	88 (13.9)	99 (12.2)	36 (6.7)	< 0.001
Hypertension	167 (29.6)	156 (22.0)	111 (20.9)	0.001
Neuropathy	60 (9.4)	82 (10.1)	44 (8.2)	0.494
Retinopathy	112 (17.6)	108 (13.3)	61 (11.4)	0.006
Nephropathy	93 (14.6)	105 (13.0)	58 (10.8)	0.151
Antipathy	51 (8.0)	62 (7.7)	25 (4.7)	0.047

Data are expressed as absolute *n* (%) or mean ± SD. [1]Up to the third generation, two sided *P* values based on one way analysis of variance with *post hoc* Tukey's test for quantitative variables and χ^2 test for categorical variables. DM: Diabetes mellitus; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; HbA1c: Hemoglobin A1c.

Table 4 Physical and clinical characteristics of patients among consanguine and non consanguine parents (*n* = 1980)

Parameters	Consanguineous (*n* = 718)				Non-consanguineous (*n* = 1262)			
	Paternal history of DM (*n* = 233)	Maternal history of DM (*n* = 323)	Without familial history (*n* = 162)	*P* value	Paternal history of DM (*n* = 402)	Maternal history of DM (*n* = 486)	Without familial history (*n* = 374)	*P* value
Age (yr)	43.9 ± 14.7	45.1 ± 15.4	47.3 ± 13.4	0.058	45.5 ± 13.6	45.1 ± 14.8	46.3 ± 13.3	0.532
BMI (kg/m^2)	27.4 ± 4.8	26.6 ± 4.9	28.1 ± 4.9	0.028	27.4 ± 5.0	26.9 ± 4.8	27.6 ± 4.8	0.428
Duration of DM (yr)	6.6 ± 3.9	7.2 ± 4.4	5.9 ± 2.9	0.004	7.2 ± 4.3	7.4 ± 4.2	6.7 ± 3.5	0.065
Metabolic characteristics								
Systolic BP (mmHg)	129.6 ± 20.4	130.7 ± 17.9	125.9 ± 11.2	0.018	130.1 ± 19.1	128.2 ± 18.1	127.8 ± 16.5	0.224
Diastolic BP (mmHg)	81.3 ± 11.4	81.1 ± 10.7	78.2 ± 8.0	0.007	81.2 ± 11.4	79.9 ± 10.4	80.0 ± 9.1	0.220
Fasting glucose (mmol/L)	10.3 ± 8.9	8.9 ± 5.0	8.9 ± 5.4	0.071	9.7 ± 9.6	9.3 ± 5.0	9.3 ± 4.3	0.689
HbA1c (%)	7.8 ± 2.1	7.7 ± 2.1	7.8 ± 2.3	0.900	8.3 ± 2.4	7.9 ± 2.2	8.3 ± 2.1	0.121
Serum urea level	5.8 ± 3.0	6.2 ± 3.2	5.9 ± 4.4	0.622	5.9 ± 2.7	6.3 ± 3.1	5.7 ± 2.8	0.170
Creatinine (mmol/L)	71.9 ± 8.5	78.0 ± 9.8	72.4 ± 9.4	0.313	75.5 ± 9.9	76.2 ± 10.2	70.9 ± 8.6	0.372
Tot. cholesterol (mmol/L)	4.9 ± 1.1	4.8 ± 1.1	4.9 ± 1.2	0.626	5.0 ± 1.2	4.8 ± 1.1	4.9 ± 1.3	0.173
Serum alkaline phosphate	92.2 ± 11.1	99.3 ± 12.8	93.5 ± 12.2	0.683	95.9 ± 12.5	102.9 ± 13.2	104.6 ± 13.5	0.460
T2DM complications, *n* (%)								
Sleep loss	44 (18.9)	40 (12.4)	12 (7.4)	0.003	44 (10.9)	59 (12.1)	24 (6.4)	0.017
Hypertension	67 (32.5)	59 (20.6)	31 (19.1)	0.002	100 (27.9)	97 (22.9)	80 (21.7)	0.114
Neuropathy	19 (8.2)	34 (10.5)	12 (7.4)	0.446	41 (10.2)	48 (9.9)	32 (8.6)	0.712
Retinopathy	44 (18.9)	41 (12.7)	13 (8.0)	0.007	68 (16.9)	67 (13.8)	48 (12.8)	0.231
Nephropathy	29 (12.4)	40 (12.4)	13 (8.0)	0.303	64 (15.9)	65 (13.4)	45 (12)	0.276
Antipathy	21 (9.0)	21 (6.5)	4 (2.5)	0.003	30 (7.5)	41 (8.4)	21 (5.6)	0.284
Hypoglycemia	62 (26.6)	91 (28.2)	46 (28.4)	0.899	111 (27.6)	113 (23.3)	99 (26.5)	0.299
Impotence	15 (6.4)	17 (5.3)	3 (1.9)	0.104	33 (8.2)	38 (7.8)	19 (5.1)	0.180

Data are expressed as absolute *n* (%) or mean ± SD. Two sided *P* values based on one way analysis of variance with *post hoc* Tukey's test for quantitative variables and χ^2 test for categorical variables. DM: Diabetes mellitus; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; HbA1c: Hemoglobin A1c; BP: Blood pressure.

Consistent with our results, a higher frequency of positive family history among mothers than fathers was reported in studies conducted in Brazil[21] (48.4% *vs* 21.3%), Britain[23] (36% *vs* 15%), France[24] (33% *vs* 17%), Greece[25] (27.7% *vs* 11%) and Tunisia[17] (21% *vs* 10%).

The present study extends the scope of genetic influence on DM by including parents, siblings, uncles, aunts and grandparents in the familial history. It was observed

that 83.7% of the diabetic patients have an affected mother and at least one relative on the maternal side, compared to only 67.3% of diabetic patients with an affected father and family member on the paternal side, suggesting a maternal transmission of T2DM in the Arab population. The excess maternal transmission of T2DM reported in this study is in line with studies from different populations with varying frequencies[3,4,18,21,25]. A positive family history of T2DM was more common among maternal aunts/uncles (31.2%) than in paternal aunts/uncles (22.2%), showing that this maternal effect likely extends to the previous generation in 2nd degree relatives, as reported in another study[21]. These study results support the existence of excess of maternal transmission of T2DM in their population. On the contrary, in the Framingham population study[26], maternal and paternal diabetes conferred equivalent risk for occurrence of T2DM in offspring. In contrast to these findings, McCarthy *et al*[27] found no difference in parental transmission of T2DM in a population with high prevalence of diabetes. Longer average life span in women could increase the likelihood that mothers develop T2DM. Fathers may have more undetected diabetes because of reduced screening rates and health care utilization or may develop diabetes at an older age than mothers.

In our study, there was an early onset of diabetes among patients with a family history of diabetes in the age group 18-30 years (24%) compared to other patients whose parents were non-diabetic (13.4%), which is similar to the results found in Greek diabetic patients[25]; this study reported that the presence of a family history of diabetes results in an early onset of the disease in the offspring. Younger age of the onset of diabetes had been noted, which implies that these subjects develop diabetes in the most productive years of their life and have a greater chances of developing complications[28]. Crispim *et al*[21] reported in their study that when the disease is diagnosed at an early age, the genetic component is more important to its development.

In the study sample, a positive family history of DM was more common among diabetic patients of consanguineous parents (77.4%) with high prevalence of maternal history (45%), whereas it was lower in patients of non-consanguineous parents (70.4%). It was reported in a recent study by Bener *et al*[10] that there was a significant increase in the prevalence of diabetes mellitus in consanguineous couples in Qatar. The current data showed that consanguinity increased the family history of DM in patients. This means that consanguinity is an important factor in the causation of diabetes mellitus in offspring.

The influence of various transmission patterns of T2DM on metabolic factors and diabetic complications have been examined. Results showed no significant difference in clinical parameters between patients with a parental or maternal history of diabetes in the study sample except for hypertension, which is similar to the study results by Bo *et al*[29]. A study in Tunisia[17] showed no significant difference in clinical parameters between patients with paternal or maternal history of diabetes in the studied sample. The development of sleep loss, hypertension, retinopathy and antipathy were significantly higher in the studied patients with a family history of DM than those without. Jali *et al*[28] found retinopathy and neuropathy less in patients with a family history of DM and risk was same in both the groups with respect to nephropathy.

Harrison *et al*[5] documented that family history information may serve as a useful tool for public health because it reflects both genetic and environmental factors. Examining family history of DM may be a valuable approach for identifying patients at risk for diabetes. In addition, this survey provides some indication that knowledge of family history of diabetes may lead to identifying people at increased risk of diabetes and perhaps motivate them to make preventive life style changes that could favorably affect both clinical practice and patient behavior.

In conclusion, the study findings showed an excess of maternal transmission of T2DM in a sample of an Arab diabetic population residing in Qatar. The data support the dominant maternal role in the development of diabetes mellitus in their offspring. No significant difference was observed between maternal and paternal diabetes in metabolic characteristics except for hypertension. Complications were higher in diabetic patients with a family history of DM. Family history of DM was higher in patients of consanguineous parents compared to non-consanguineous parents. The presence of a family history of diabetes resulted in an early onset of the disease of the offspring. Interventions to change life style habits among families might reduce the risk of diabetes in the offspring of diabetic patients.

ACKNOWLEDGMENTS

The authors would like to thank the Hamad Medical Corporation for their support and ethical approval (ref: RP 10067/10).

COMMENTS

Background

Diabetes is a disease that has a strong clustering in families and has a genetic component. Family history is a well-known risk factor for developing type 2 diabetes mellitus (T2DM). The high incidence of consanguineous marriages in the State of Qatar highlighted the importance of determining the influence of familial history of T2DM in the offspring.

Research frontiers

The study indicated that knowledge of family history of diabetes may lead to identifying people at increased risk of diabetes. The study highlighted the importance of identifying this high risk group and make preventive life style changes which might reduce the risk of diabetes in offspring.

Innovations and breakthroughs

The important study findings of this article are compared to studies conducted regionally and internationally which make the readers understand the high prevalence of diabetes mellitus in a consanguineous population.

Applications

This will encourage the researchers in this region to explore the paternal transmission of T2DM in their community and conduct intervention studies to change life style habits among families.

Peer review

The authors recommended through this study that family history information may serve as a useful tool for public health because it reflects both genetic and

environmental factors. Physicians should consider the family history of diabetes mellitus to identify the onset of DM in their offspring.

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World J Diabetes 2013 April 15; 4(2): I-V
ISSN 1948-9358 (online)

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Name of journal

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

Frequency

Bimonthly

Editor-in-chief

Editorial office

World Journal of Diabetes
Editorial Department: Room 903, Building D,
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Chaoyang District, Beijing 100025, China
E-mail: wjd@wjgnet.com
http://www.wjgnet.com
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Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
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Production center
Beijing Baishideng BioMed Scientific Co., Limited
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
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