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EDITORIAL

Pharmacologic adjunctive to insulin therapies in type 1 diabetes: The journey has just begun

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Abstract

Treatment of type 1 diabetes (T1D) is currently based exclusively on insulin replacement therapy. However, there is a need for better glycemic control, lower hypoglycemia rates, more effective weight management, and further reduction of cardiovascular risk in people with T1D. In this context, agents from the pharmaceutical quiver of type 2 diabetes are being tested in clinical trials, as adjunctive to insulin therapies for T1D patients. Despite the limited amount of relevant evidence and the inter-class variability, it can be said that these agents have a role in optimizing metabolic control, assisting weight management and reducing glycemic variability in people with T1D. Specific safety issues, including the increased risk of hypoglycemia and diabetic ketoacidosis, as well as the effects of these treatments on major cardiovascular outcomes should be further assessed by future studies, before these therapeutic choices become widely available for T1D management.

Key words: Type 1 diabetes; Insulin; Adjunctive therapies; Cardiovascular risk

Core tip: Adjunctive to insulin therapies in type 1 diabetes (T1D) may have a role in optimizing metabolic control, assisting weight management and reducing glycemic variability. Specific safety issues should be further assessed by future studies, before these therapeutic choices become widely available for T1D management.

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INTRODUCTION

Treatment of type 1 diabetes (T1D) is currently based exclusively on insulin replacement therapy, either by multiple daily injections (MDI) or *via* continuous subcutaneous insulin infusion ("insulin pumps") and closed-loop (also known as "artificial pancreas") insulin delivery systems. Whole pancreas and islet cell transplantations are alternative therapeutic options for carefully selected patients meeting specific eligibility criteria; still, these procedures are available only in a few number of specialized centers around the world, thus, being unavailable for the vast majority of people living with T1D[1].

The idea of using agents from the pharmaceutical quiver of type 2 diabetes (T2D) as adjunctive to insulin therapies in T1D is not recent; back in 1985, Gin *et al*[2], published their research on the effects of metformin on insulin sensitivity in patients with T1D and since then, a number of agents from different therapeutic classes have been tested in clinical trials. In the present article, we aim to discuss the rationale behind the use of adjunctive therapies in T1D, strengths and limitations of such an approach, as well as gaps in existing knowledge that deserve further evaluation by future research.

WHY IS THERE A NEED FOR ADJUNCTIVE THERAPIES IN T1D?

We live in the era of long- and short-acting insulin analogues (and the very recently introduced ultra-fast acting insulin analogues), which mimic physiological insulin release in a more effective way than human insulin, resulting in better metabolic control and lower hypoglycemia rates, as compared to the latter[3]. Hence, what would adjunctive to insulin treatments contribute more to T1D management in everyday, clinical practice?

First, despite the progress been made during the past years, there is still an imperative need for better glycemic control in people with T1D. Results from a multi-centre, observational, cross-sectional study from Central and Eastern Europe (DEPAC Survey), involving more than 10000 individuals, proved that only 13.1% of T1D patients had glycated hemoglobin $A1_c$ ($HbA1_c$) levels within target (< 6.5% / 47.5 mmol/mol)[4]. Mean $HbA1_c$ concentration among participants was 8.2% (66.1 mmol/mol), ranging from 7.7% (60.7 mmol/mol) to 9.8% (83.6 mmol/mol) among different countries.

Secondly, it is well established that people with T1D are in a greater risk of developing atherosclerotic disease, compared to the general population[5]. Data from the United Kingdom General Practice Research Database (UK GPRD), indicate a hazard ratio for major cardiovascular disease (CVD) event (myocardial infarction, acute coronary heart disease death, coronary revascularizations, or stroke) of 3.6 (95%CI: 2.9-4.5) in men with T1D and of 7.7 (95%CI: 5.5-10.7) in women with T1D, compared to people without diabetes[6]. Considering the impressive cardioprotective effects that specific agents used in T2D management have demonstrated in recent, randomized clinical trials[7], it is reasonable to consider that these outcomes could be also applicable in T1D populations; however, this is something that remains to be proven by future research.

Thirdly, insulin resistance and adipose tissue inflammation as a result of increased body weight, are key components of T2D pathogenesis[8]. A number of novel agents for T2D management, including glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter 2 (SGLT-2) inhibitors, exert optimal effects on body weight, through a variety of acting mechanisms[9]. However, obesity is being increasingly recognized as a major health problem among people with T1D, as well. Results from a prospective study from the United States, where participants with T1D were being followed for a median of 18 years, demonstrated that overweight increased by 47% and the prevalence of obesity increased 7-fold during the above period, with 22.7% of people with T1D having body mass index (BMI) equal or greater to 30 kg/m^2[10], at the end of the study. In the same study, only seven percent of patients were on intensive insulin therapy (three or more daily insulin injections) at baseline (1986-1988), in contrast with the end of the follow-up period (2004-2007),

when this percentage reached 82%. Therefore, the aforementioned results could be attributed to the increasing rate of the adoption of a "Western" dietary model combined with poor physical activity by a significant proportion of the population worldwide, along with the intensification of insulin therapy during the last decades, which is known to positively correlate with weight gain[11]. It is also known that weight, insulin resistance and CVD risk significantly interplay in people with diabetes. In a prospective cohort study following 603 patients with T1D for 10 years, classic insulin resistance-related factors, including dyslipidemia and waist-to-hip ratio, were found to predict future coronary artery disease events[12], suggesting a strong need for effective management of traditional CVD risk factors, apart from T2D, in T1D as well.

There is data suggesting limitations in insulin availability and affordability in specific areas of the world, particularly for low-income patients[13]. Reduction of insulin dose as a result of adjunctive therapies may prove helpful for those who consider insulin cost as a significant barrier to treatment adherence. Finally, there is no doubt that intensive compared to conventional glycemic control results in lower rates of both micro- and macro-vascular complications in individuals with T1D[14]. However, this can be only achieved at a cost of increased incidence of hypoglycemia[15], which is known to be related with cardiac dysrhythmias, CVD events and death[16]. As a result, clinicians are often required to navigate "through stormy waters" and balance their clinical practice between intensive metabolic control and hypoglycemia, in a way that is not always easy.

AN OVERVIEW OF AVAILABLE EVIDENCE

Considering the above, there is an increasing amount of evidence suggesting that adjunctive to insulin treatments may assist glycemic control and weight management in T1D. Metformin has been shown to manifest optimal effects on BMI, total and low-density lipoprotein cholesterol concentrations, and total daily insulin dose (TDD), still not on $HbA1_{C,}$ which following a transient reduction during the first months of therapy, returns to its baseline values[17]. The REMOVAL trial aimed to explore the effects of metformin on carotid intima media thickness (cIMT) in a sample of 428 T1D patients with multiple cardiovascular risk factors, aged over 40 years[18]. Progression of mean cIMT was not significantly reduced with metformin, although maximal cIMT was significantly lower in the metformin group, as compared to placebo. Furthermore, metformin use has been linked to an increasing trend of the incidence of hypoglycemia[19], a clue that requires further assessment by additional studies, particularly with the use of Continuous Glucose Monitoring systems. Overall, existing data do not support that metformin may improve glycemic control, though it might have a wider role in reducing CVD risk in people with T1D.

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been tested in a very small numbers of trials and safe conclusions regarding these agents cannot be drawn. Their impact on glycemic control, seems to be non-significant[20]; nevertheless, there is preliminary data indicating that sitagliptin might lower postprandial glucose levels in patients treated with a closed-loop system[21] and preserve beta-cell function in individuals with slowly progressive T1D[22]. In addition, DPP-4 inhibitors probably exert some important immunoregulatory actions[23], thus, deserving further evaluation as adjunctive treatments in T1D or other autoimmune types of diabetes [Latent Autoimmune Diabetes in Adults (LADA), for example].

GLP-1 agonists have been demonstrated to significantly reduce $HbA1_{C,}$ body weight and TDD (particularly bolus doses), when used in people with T1D[24]. However, some studies raised concerns regarding their safety. In ADJUNCT ONE trial, 1398 patients with T1D were randomized to receive either liraglutide at varying doses or placebo, on top of insulin whose dose was adjusted according to a treat-to-target protocol over 52 wk[25]. Symptomatic hypoglycemia was increased in all liraglutide groups as compared to placebo. Hyperglycemia with ketosis was more frequent in the group of patients receiving liraglutide at 1.8 mg, probably due to nausea related to its use and concomitant reduction of insulin dose. Similar reductions in $HbA1_{C,}$ BMI and insulin dose have been observed with pramlintide, an injectable synthetic amylin analogue, being the only drug approved by the United States Food and Drug Administration, as an adjunctive to insulin therapy in T1D[26]. Its use in everyday practice is limited by the fact that it should be subcutaneously administered three to four times a day before meals, being nonpractical for patients already on MDI regimens.

Probably, the most promising results in the field are coming from studies conducted with SGLT-2 inhibitors. These agents seem to contribute to better glycemic

control, lower body weight and insulin dose and most importantly, without increasing hypoglycemia rates[27]. In addition, preliminary evidence suggests that they reduce glycemic variability[28], a parameter that is being increasingly recognized to be related to the development of diabetic complications[29]. On the other hand, a systematic review and meta-analysis of ten studies using SGLT-2 inhibitors on top of insulin in T1D, pointed towards an increased risk of diabetic ketoacidosis (DKA) in patients treated with these agents versus placebo[27]. The review identified 16 incidents of both hyperglycemic and normoglycemic DKA in a total of 581 patients. Similar to the clinical experience from the use of SGLT-2 inhibitors in people with T2D, a consistent increase in the incidence of genital tract infections, particularly among females, has been documented in individuals with T1D, as well[30]. As a result, gains and risks should be carefully balanced prior to the use of these drugs in everyday practice. Table 1 summarizes the main advantages and pitfalls of the use of various therapeutic classes as adjunctive treatments in T1D.

A CRITICAL APPRAISAL OF RELEVANT STUDIES

The aforementioned results should be interpreted with caution, given that relevant data manifest specific weaknesses. First, the number of studies and patients involved is limited, rendering the extraction of definite conclusions challenging. Secondly, most of relevant studies have been designed to explore "conventional" outcomes, such as changes in $HbA1_C$, body weight and insulin dose. Data on glycemic variability, insulin resistance and oxidative stress markers are scarce, being inversely proportional to the significance that these parameters are gradually gaining, regarding their contribution to the development of diabetes complications.

Moreover, all of these studies are considering people with T1D as an homogenous group of patients, who will overall get - or not get - benefit from adjunctive therapies[31]. It is well established that some people with autoimmune diabetes (either long-term T1D or LADA) share common pathophysiological and phenotypic features with T2D, thus, being difficult to draw the borderline between distinct diabetes types, in these cases[32]. The need for individualized treatment approaches is emphatically highlighted by the paradigm of thiazolidinedione use in T1D; when pioglitazone was added on insulin in lean adolescents with T1D, it had no remarkable effect on glycemic control. In contrast, it resulted in a significant weight gain (+ 3.8 kg), as compared to placebo[33]. Differently, rosiglitazone significantly decreased both $HbA1_C$ and TDD, when it was administered in overweight subjects with T1D, where insulin resistance had an apparently important pathogenetic role in the development of metabolic disarrangement[34].

Finally, trials with "hard" CVD end points in T1D populations are currently lacking, being necessary to clarify whether the remarkable effects of specific agents on CVD morbidity and mortality in people with T2D, can be translated to respective CVD benefits in people with T1D. Table 2 summarizes the main limitations of available evidence on the use of various drugs as adjunctive treatments in T1D.

FUTURE CLINICAL RESEARCH STUDIES

Despite the initial enthusiasm for potential clinical implications of immunotherapy in T1D, research in the field has so far failed to prevent the onset or to reverse autoimmune diabetes[35]. Stem cell therapies, immune ablation and standard immunosuppressants have been tested in several studies, nevertheless not being able to confirm the expectations derived from animal models, at least for the moment. Immune prevention strategies have tested low insulin doses and alternative administration routes (*e.g.*, oral insulin) to prevent diabetes in individuals at high risk of T1D, still showed no remarkable benefit[36]. Studies using non-antigen specific immunosuppressive drugs demonstrated encouraging results in prolonging remission of T1D; however, at a cost of toxicity and side effects[37]. Leptin might prove useful in suppressing glucagon concentrations[38], but clinical benefits of its use in T1D should be further evaluated by clinical trials. As a result, safety and efficacy of these treatments in T1D remain an area for forthcoming studies.

CONCLUSION

In conclusion, despite the limitations of available evidence and the inter-class variability, adjunctive to insulin therapies may have a role in optimizing metabolic

Table 1 Advantages and pitfalls of the use of various therapeutic classes as adjunctive treatments in type 1 diabetes

Therapeutic class	Advantages	Pitfalls
Biguanides (metformin)	Optimal effects on body weight, lipid concentrations and insulin dose	Effect on $HbA1_C$ not sustainable over time. Potentially greater risk of hypoglycemia
DPP-4 inhibitors	Immunoregulatory actions. Potential role in preserving beta-cell function. Good safety profile	Non-significant effect on $HbA1_C$
GLP-1 agonists	Significant reductions in $HbA1_C$, body weight and insulin dose (particularly bolus doses)	Greater risk of hypoglycemia and DKA
Amylin analogues (pramlintide)	FDA approved. Significant reductions in $HbA1_C$, body weight and insulin dose (particularly bolus doses)	It should be subcutaneously administered 3-4 times/d
SGLT-2 inhibitors	Optimal effects on $HbA1_C$, body weight, insulin dose and glycemic variability. They do not increase risk of hypoglycemia	Increased risk of DKA and genital tract infections
Thiazolidinediones	Reduction in $HbA1_C$ and insulin dose in insulin-resistant T1D patients	Weight gain. Not effective in lean patients

$HbA1_C$: Glycated hemoglobin $A1_C$; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; FDA: United States Food and Drug Administration; SGLT-2: Sodium-glucose co-transporter 2; T1D: Type 1 diabetes; DKA: Diabetic ketoacidosis.

control, assisting weight management and reducing glycemic variability in people with T1D. Specific safety issues, including the increased risk of hypoglycemia and DKA, as well as the effects of these treatments on major cardiovascular outcomes should be further assessed by future studies, before these therapeutic choices become widely available for T1D management. It seems that for both physicians and people with T1D, a fascinating journey to the land of pharmacologic adjunctive to insulin therapies has just begun.

Table 2 Main limitations of available evidence on the use of various drugs as adjunctive treatments in type 1 diabetes

Limitations of clinical trials	Small number of studies and patients involved
	Heterogeneity in study designs and explored outcomes
	"Conventional" outcomes explored: changes in $HbA1_C$, body weight and insulin dose. Data on glycemic variability, IR and OS markers are scarce
	Not taking into account the clinical heterogeneity of patients with T1D
	Trials exploring the effects of adjunctive treatments on "hard" CVD end points in T1D patients are currently unavailable

$HbA1_C$: Glycated hemoglobin $A1_C$; T1D: Type 1 diabetes; CVD: Cardiovascular disease; IR: Insulin resistance; OS: Oxidative stress.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors in patients with type 2 diabetes in Bengaluru: A retrospective study

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Abstract

BACKGROUND

Risk factors such as hereditary, ecological, and metabolic are interrelated and contribute to the development of type 2 diabetes mellitus. Family history (FH) of diabetes mellitus, age, obesity, and physical inactivity are some of the risk factors for the development of type 2 diabetes.

AIM

To study various aetiological determinants and risk factors for type 2 diabetes in Bangalore, India. This retrospective study examined questionnaire from patients attending the Diabetes Clinic.

METHODS

Data on various parameters were obtained through a questionnaire from 533 patients on the first visit to the diabetes clinic. Data regarding various aetiological determinants and risk factors *viz*.: Genetic risk factor and few modifiable risk factors were collected. Chi-squared test was used for statistical analysis.

RESULTS

A higher incidence of type 2 diabetes in males and younger population was observed in Bangalore, India. Obesity and FH were significant risk factors for not only type 2 diabetes but also early onset of diabetes. In addition, maternal history of type 2 diabetes and consanguinity increased incidence of early onset type 2 diabetes.

CONCLUSION

Risk factors such as obesity and FH (maternal history of type 2 diabetes) and consanguinity may play an important role in screening of family members of type 2 diabetes patients which may lead to early intervention and reduced risk of subsequent complications. Moreover, susceptible population can be counselled for the management of the type 2 diabetes including periodic investigation of blood glucose levels and lifestyle changes.

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Key words: Type 2 diabetess mellitus; Young onset diabetes; Family history; Consanguinity; Diabetes risk factors; Obesity

Core tip: Obesity, family history, maternal history of type 2 diabetes, and consanguinity play an important role in increasing incidence of early onset type 2 diabetes and should be used as parameters in screening of patients for type 2 diabetes. This may aid in initiating early life style changes to delay the onset of disease and/or reduce its severity. It may also lead to early diagnosis in high risk patients.

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INTRODUCTION

According to International Diabetes Federation (IDF) Diabetes Atlas eighth edition 2017, the IDF South-East Asia region is at the epicentre of the diabetes crisis which includes India at the second position behind China with a diabetes population of 82 million. In 2017, there were more than 72946400 cases of diabetes in India. As per the IDF estimates India would gallop to the first position with a diabetes population of 151 million by 2045[1].

Hereditary, ecological, and metabolic risk factors contribute to the development of type 2 diabetes mellitus (T2DM) and are interrelated. Higher risk of diabetes with a family history (FH) of diabetes mellitus, age, obesity, and physical inactivity has been identified. Influence of dietary habits and lifestyle are critical and are responsible for higher occurrence and prevalence of obesity and diabetes in the urban population[2,3]. In addition, individuals with T2DM are often accompanied with co-morbid conditions such as cardiovascular diseases, diabetic neuropathy, nephropathy, and retinopathy[4]. This imminent crisis warrants study of aetiology and risk factors in the "real world" medical practice. "Real world" practice environment is an invaluable source of information and may reveal important trends in the aetiology, management, and treatment of diseases in "real world" medical practice.

Bearing in mind the need to preserve the naturalistic environment and manage with available staff resources for compiling data in the busy medical practice setting and yet generate meaningful conclusions. We at our diabetes centre initiated a data collection drive in form of a questionnaire. Our objective for the retrospective analysis was to gain insights into the patient profile and associated risk factors.

MATERIALS AND METHODS

Patients

This is a retrospective analysis of information obtained from patients with T2DM diagnosis attending the outpatient department (OPD) from July 2016 to July 2017. The patients who visited our OPD for the first time were required to complete a questionnaire. Our staff assists the incapable patients in completing the questionnaire. With the help of the questionnaire, information regarding various aetiological determinants and risk factors were sought namely: genetic risk factor–FH, demographic characteristics- age, gender, and ethnicity and among modifiable risk factors- obesity and physical inactivity.

The bases of categorising patients in different groups are described as follow: (1) FH: It includes information on history of T2DM in either or both parents or a first degree relative, accordingly they were classified as either positive with FH (FH+) or no FH (FH-) of diabetes mellitus; (2) Proposed classification of weight by body mass index (BMI) in adult Asians[5]: < 18.5 kg/m^2: Underweight; 18.5–22.9 kg/m^2: Normal BMI; ≥ 23 kg/m^2: Overweight; At risk 23-24.9 kg/m^2 increased; Obese I 25-29.9 kg/m^2 moderate; Obese II ≥ 30 kg/m^2 severe; (3) Physical activity: "Sedentary" was defined as patients who neither exercised nor walked at all. Among these, patients who were

working had a sedentary job profile. "Strenuous" was defined as people who did some form of exercise like walking, jogging, were trained for marathons or whose job involved significant physical activity like labourers, sales personnel, *etc*.

Statistical analysis

Chi-squared test as recommended by Campbell and Richardson was used. The confidence interval was calculated[6].

RESULTS

Information on various parameters described above was obtained from 533 patients. Among these type 1 diabetes (n = 2), gestational diabetes mellitus (n = 1), chronic pancreatitis (n = 1), prediabetes (n = 6) those with no diagnosis of T2DM (n = 2), incomplete information (n = 2) were excluded. Thus, of the 533 questionnaires obtained, 519 were considered evaluable based on the information provided. The overall characteristics of patients are listed in Table 1.

Gender

Compared to females the proportion of male patients diagnosed with T2DM was significantly higher (55.68% *vs* 44.12%; P = 0.0002).

Obesity

Among 519 patients the information on BMI was available for 479 patients. It was noted that the patient population diagnosed with T2DM was significantly overweight or obese (88.30% *vs* 11.69%; P < 0.0001). In patients in the age group up to 40 years, the prevalence of obesity and diagnosis of T2DM was higher in males than females (80.76% *vs* 77.27%); whereas in patients 41-50 years the proportion was reverse (females *vs* males; 85.39 *vs* 79.31).

Physical activity

Among the patients who were diagnosed with T2DM, significantly higher proportion of patients followed a sedentary lifestyle compared to a strenuous one (74.89% *vs* 25.10%; P < 0.0001). Across the age groups the proportion of patients with a sedentary lifestyle or occupation was significantly higher compared to strenuous. However, even in patients in the latter group, obesity was prevalent; probably due to a diet conducive to weight gain (Table 2).

FH

Among 519 patients, 308 (59.34%) had a FH+ of diabetes. Compared to paternal, the maternal positive FH was higher in patients diagnosed with T2DM (59.68% *vs* 49.52%).

Risk factors for early onset type 2 diabetes

The patients were categorised into five age groups according to the age of onset of type 2 diabetes. It was noted that the proportion of patients with onset of diabetes at younger age groups (≤ 40 years and 41-50 years) was significantly higher, almost twice compared to older age groups (51 to ≥ 70 years) (Table 3).

Further subgroup analysis demonstrated that in the 125 patients with new onset or recent (< 3 mo) onset of diabetes in the one year study period (July 2016-2017), the proportion patients with young onset diabetes [YOD (aged ≤ 40 years)] was numerically the highest (Table 4).

FH

Among 519 patients, 308 had a FH+ of diabetes. Of these 39.93% patients were ≤ 40 years whereas those with FH- the percent patients with YOD were almost half (39.93% *vs* 20.85%, P < 0.0001) (Table 5). In non-obese, T2DM patients diagnosed early, about 80% had a FH+. On exclusion of consanguinity cases, 28.57% demonstrated FH+ as a risk factor. However, consanguinity was not a significant independent risk factor in non-obese patients since all consanguineous cases had positive FH (Table 6).

Effect of consanguinity

Among 506 patients for whom the consanguinity data was available, 141 patients reported consanguineous marriages of first-degree cousins (CG+). When these patients were grouped according to age of onset of diabetes, YOD was noted in approximately 35% patients. Also between age group comparison in CG+ patients indicated that, age group 1 (age ≤ 40 years) had almost twice as patients with T2DM than (CG+) age group 3 (age 51-60 years). After adjusting for obesity as a risk factor,

Table 1 Demographic characteristics of outpatient department patients diagnosed with type 2 diabetes mellitus included in the retrospective analysis

Characteristics	*n* (%)
Total patients	519
Male	289 (55.68)
Female	229 (44.12)
Transgender	1 (0.19)
Average age (yr)	53.28
Ethnicity	Indian

the consanguinity parameter was still a significant risk parameter for developing early onset diabetes (age ≤ 40 years) (CI: 1.7293 to 23.3104; $P = 0.0178$) (Table 7). For the remaining age groups, there was no significant difference between consanguinity and obesity as a risk factor for onset of T2DM.

Effect of hypothyroidism

Among female patients, hypothyroidism did not demonstrate any significant impact on age of onset of diabetes.

DISCUSSION

Gender roles and gender identity are influenced by a complex relationship between genetic, endocrine, and social factors[7]. Gender is a vital genetic factor in regulation of homeostasis and affects susceptibility to cardio-metabolic risk factors. It also influences management of T2DM. Previous studies have demonstrated inconsistent gender distribution among patients diagnosed with T2DM. In 2013, IDF reported that there were 14 million times more men affected with diabetes than women[8]. Studies in Northern India show female predominance whereas data from Southern India have reported higher prevalence in males. Few others have found no gender inclination in prevalence of T2DM[9]. Data from our retrospective analysis reaffirm the higher prevalence of T2DM in males in Southern India. Men apparently are more disposed than women to the consequences of inactivity and obesity, conceivably due to variances in insulin sensitivity and regional fat deposition[10].

Several studies have shown a high prevalence of abdominal obesity and generalized obesity as evaluated by body fat percentage in type 2 diabetic individuals[11,12]. Approximately 44% of the diabetes burden, is attributable to overweight or obesity[13]. In the current study, obesity was a major risk factor for T2DM similar to the findings in previous studies. The data showed that the proportion patients with T2DM being obese or overweight patients was eight times higher than patients who were non-obese/non-overweight. The proposed mechanisms linking the two are increased production of adipokines/cytokines, which may lead to insulin resistance and decrease in levels of adiponectin, ectopic fat deposition, mitochondrial dysfunction which not only decreases insulin sensitivity but also affects β-cell function[14].

Apart from genetics, obesity is rooted primarily in improper diet or physical inactivity, however in the current study we observed that even in patients who had an active or strenuous lifestyle the prevalence of obesity was comparable to the sedentary group. This may imply that the nutritional transition, to highly-saturated fats, sugar, and refined foods and the transport facilities and increased stress, particularly in the urban populations may play an important role[15].

A FH of diabetes is related with a range of metabolic abnormalities and is a strong risk factor for the development of T2DM. The elevated risk of T2DM is mediated, at least in part, by both genetic and common environmental components amongst family members[15]. In our study more than half of the patients diagnosed with T2DM indicated FH+ of diabetes. Also the risk is greater with maternal than paternal FH, the findings in our study substantiate the same since approximately 10% higher risk was noted in patients with positive maternal FH.

Further subgroup analysis according to the influence of factors discussed previously on early onset T2DM showed that the proportion of patients diagnosed with T2DM in the younger age group (≤ 40 years -50 years) was twice as high than the older patient group (> 50 years), $P < 0.0001$.

Subgroup analysis of our data demonstrated that in the patients with new onset or

Table 2 Proportion of patients based on physical activity: Sub grouped based on body mass index

Groups	Age range (Y)	Sedentary (%)	Obese/OW (%)	Strenuous (%)	Obese/OW (%)	Sedentary *vs* strenuous *P*
Group 1	≤ 40	68.00	75	31.90	84.61	< 0.0001
Group 2	41-50	75.60	80.64	24.39	87.50	< 0.0001
Group 3	51-60	77.35	78.04	22.64	91.66	< 0.0001
Group 4	61-70	87.50	100	12.50	100.00	< 0.0001
Group 5	> 70	83.33	50	16.66	50.00	< 0.0001

OW: Overweight.

recent (< 3 mo) onset of diabetes in the one year study period (July 2016-2017), the proportion patients with YOD (aged ≤ 40 years) was numerically the highest compared to other age groups and significantly higher in patients in the age groups < 40-50 years compared to patients in the age group of > 50 years. Like it was pointed out in the discussion regarding FH+ the proportion of patients with FH+ were twice at higher risk of YOD than FH-, which reconfirms that FH+ could be an important factor increasing susceptibility to YOD.

Even in absence of obesity as a risk factor, FH+ had a significant influence on YOD with more than 80% with documented FH+. However, consanguinity was not a significant independent risk factor in non-obese patients. After adjusting for obesity as a risk factor, the consanguinity parameter was still a greater risk parameter for developing early onset diabetes (age ≤ 40 years).

Type 2 diabetes and its related complications enforce heavy health burdens worldwide and there have been not effective measures to fully manage with the diseases. T2DM affecting almost all populations in both developed and developing countries with high rates of diabetes-related morbidity and mortality. Multiple risk factors mainly obesity, FH specifically maternal history of type 2 diabetes and consanguinity play an important role to development of T2DM. To overcome these risk factors, screening of patient's family members is essential to identify in early stage and conquer this disease and improve the quality of life with increases in overall life span of individuals.

Strengths and limitations

We have used subjects of verified incident diabetes mellitus cases within south region of India (Bengaluru). The diversity of the cohort in terms of lifestyle and social characteristics due to metropolis city allows a robust assessment of the risk factors for diabetes mellitus. However, there are some limitations in this study. We used retrospective data that lacked detailed patient's information in detail on lifestyle as well as physical, hereditary, and some laboratory parameters. We have tried to use all possible parameters that define the risk factors most accurately. However, more detailed information on large set of population in future studies can help understand the risk of diabetes.

Table 3 Distribution of patients according to age of onset of type 2 diabetes mellitus

Age at onset of diabetes (yr)		%	*P* value
Group 1	≤ 40	32.30	0.0001 Group 1 *vs* 3 < 0.0001 Group 1 *vs* 4 < 0.0001 Group 1 *vs* 5
Group 2	41-50	34.04	< 0.0001 Group 2 *vs* 3 < 0.0001 Group 2 *vs* 4 < 0.0001 Group 2 *vs* 5
Group 3	51-60	21.27	
Group 4	61-70	12.18	
Group 5	> 70	0.21	

Table 4 Age at new onset (< 3 mo) of diabetes (years)

Age at new onset (< 3 mo) of diabetes (yr)		*n* (%)
Total new T2DM diagnosis		97
Group 1	≤ 40	32 (32.98)
Group 2	41-50	27 (27.83)
Group 3	51-60	25 (25.77)
Group 4	61-70	7 (7.21)
Group 5	> 70	6 (6.18)

T2DM: Type 2 diabetes mellitus.

Table 5 Association of family history and age of young onset diabetes

Parameter	FH+	FH-	*P* value
FH *n* (%)	308 (59.34)	211 (40.65)	< 0.0001
Age of onset ≤ 40 yr (%)	39.93	20.85	< 0.0001

FH+: Positive family history; FH-: No family history.

Table 6 Association of Family history, consanguinity and young onset diabetes

Risk factor	Non obese T2DM patients (%)		*P* value
FH+	80	20	*P* < 0.0001
CG+	51.42	48.57	NS

T2DM: Type 2 diabetes mellitus; FH+: Positive family history; CG+: First-degree cousins.

Table 7 Association of consanguinity and young onset diabetes

Age group	T2DM patients (%)	T2DM obese patients (%)	
≤ 40 yr	34.50	21.83	*P* = 0.0178
51-60 yr	17.60	14.78	NS
	P = 0.0012	NS	

T2DM: Type 2 diabetes mellitus; NS: Not siginificant.

ARTICLE HIGHLIGHTS

Research background

The highest risk of diabetes with a family history (FH) of diabetes mellitus, age, obesity, and physical inactivity were identified. Influence of dietary practices and lifestyle factors are critical, making occurrence and prevalence of obesity and diabetes significantly more in the urban

population. As per the International Diabetes Federation estimates India would gallop to the first position with a diabetes population of 151 million by 2045.

Research motivation
"Real world" practice environment is an invaluable source of information and reveals important trends in the "real world" medical practice.

Research objectives
Our diabetes centre initiated a data collection drive in form of a questionnaire. Our objective for the retrospective analysis was to gain insights into the patient profile and associated risk factors.

Research methods
Information was obtained through a questionnaire from patients on their first visit to our diabetes clinic. Information regarding various aetiological determinants and risk factors *viz*.: Genetic risk factor and few modifiable risk factors was sought. Chi-squared test is used for statistical analysis.

Research results
Statistical analysis of the organized information obtained indicated a higher incidence of type 2 diabetes in males and younger population. Obesity, FH was significant risk factors for not only type 2 diabetes but also early onset of diabetes. In addition, maternal history of type 2 diabetes and consanguinity were found to play an important role in increasing incidence of early onset type 2 diabetes.

Research conclusions
Particular attention to risk factors like obesity, FH specifically maternal history of type 2 diabetes and consanguinity may be important for screening of patient's family members to initiate early intervention and reduce risk of subsequent complications. Moreover, susceptible population can be counselled regarding the risk, periodic investigation of blood glucose levels and lifestyle changes.

Research perspectives
Multiple risk factors mainly obesity, FH specifically maternal history of type 2 diabetes and consanguinity play an important role to development of type 2 diabetes mellitus. To overcome this risk factors, screening of patient's family members is essential to identify in early stage and conquer this disease and improve the quality of life with increases in overall life span of individuals.

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Observational Study

Management and control of type 2 diabetes mellitus in Lebanon: Results from the International Diabetes Management Practices Study Wave 6

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Abstract

BACKGROUND

Diabetes mellitus is a worldwide public health problem associated with significant complications. There is lack of data on the quality of care of patients with diabetes, specifically among the non-Western countries. Efforts have been made in Lebanon to better study the characteristics of patients with diabetes mellitus in order to improve glycemic control and prevent late-term complications.

AIM

To investigate control and therapeutic management of patients with diabetes mellitus in the current medical practice in Lebanon.

METHODS

Wave 6 of the International Diabetes Management Practice Study in Lebanon is an international and multicenter study involving selected countries.

RESULTS

Only 1 patient with type 1 diabetes and 595 patients with type 2 diabetes were included in Wave 6. Average age was around 60 years, with a mean body mass index of 30. The mean fasting serum glucose was 159.42 mg/dL, and the mean glycosylated hemoglobin (HbA1c) level was 7.98 with around 30% achieving an HbA1c target of < 7%. More patients were on oral anti-diabetic medications. Screening of diabetic complications has improved over the years. A large percentage is diagnosed with hypertension and dyslipidemia, the majority of

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whom were treated but only a small percentage were controlled.

CONCLUSION
Diabetes, with its associated dyslipidemia and hypertension, is still not very well controlled. Screening for diabetes complications has improved over the years. Patients need to have more proper care, and physicians need to follow diabetes guidelines, and to have a larger number of patients who have appropriate treatment of diabetes, hypertension and lipids.

Key words: Diabetes complications; Dyslipidemia; Hypertension; Blood pressure control; Glycemic control

Core tip: This paper assessed the therapeutic management and control of patients with diabetes mellitus in the current medical practice in Lebanon. It also identified the proportion of subjects with target glycosylated hemoglobin, good blood pressure and lipid control, showing that it was suboptimal. Screening of diabetes-related complications is improving. Treating physicians and caregivers are becoming more aware of the importance of screening, but despite all their efforts, glycemic and metabolic control of the Lebanese type 2 diabetes mellitus population is still suboptimal.

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INTRODUCTION

Diabetes mellitus is a major public health issue worldwide that is associated with significant complications. The International Diabetes Federation (IDF) estimated that there would be an increase in the number of patients with diabetes worldwide, from 592 million persons in 2015 to 642 million in 2040[1]. This rise is expected to be greatest in developing countries[2]. In Lebanon, the prevalence of diabetes was found to be 7.8% for the population aged 20-79 years[3]. A strong positive correlation was found between type 2 diabetes and both higher body mass index (BMI) and sedentary lifestyle[4]. There is a lack of data on the quality of care of patients with diabetes, specifically among non-Western countries.

In Lebanon, a study demonstrated that glycosylated hemoglobin (HbA1c) was only reported in 40% out of the 204 diabetic patients assessed, with controlled diabetes (HbA1c < 7%) in 28.4%, and an HbA1c ≥ 8.5% in 38.3%[5]. In addition, a high prevalence of micro-vascular diabetic complications was found among Lebanese with diabetes, with at least one third having neuropathy or retinopathy, and almost 50% having albuminuria. As for macro-vascular complications, 20% were found to have coronary artery disease and peripheral vascular disease (PVD), and 4.1% had cerebrovascular disease[6]. Therefore, there is a need to better assess the current practices in diabetes management, and put some action into place in order to improve the quality of care for these patients. This is especially important for patients from both the United Kingdom Prospective Diabetes Study[7] carried out on type 2 diabetes mellitus patients, as well as the Diabetes Control and Complications Trial[8] carried out on type I diabetes patients, which showed that tight glucose control can prevent the onset and progression of microvascular complications to a significant extent. In the long-term, it can even prevent cardiovascular events, as was shown in their follow-up studies[9,10].

In recognition of this, the International Diabetes Management Practices Study (IDMPS) was set to collect data in a standardized manner in order to primarily assess the therapeutic management and control of type 2 diabetes mellitus in the current medical practice in the Lebanese population, and reflect on the characteristics of Lebanese patients with type 2 diabetes. Previously, data were reported in Lebanon between the years 2006 and 2012[11,12]. In this paper, data from Wave 2013-2014 of the

IDMPS were retrieved and analyzed. Secondary endpoints included the proportion of subjects with target HbA1c in compliance with the international recommendations' guidelines[13,14], the frequency of hypoglycemia episodes, and the assessment of the health economic impact of type 2 diabetes and its complications.

MATERIALS AND METHODS

The IDMPS is an international, observational study conducted in multiple selected centers in different non-Western countries. This study included patients with type 1 and type 2 diabetes mellitus, who were selected in a random fashion from a representative pool of diabetic patients. The IDMPS consisted of six waves, beginning in the year 2006 and ending in 2014, with each wave being conducted yearly and consisting of a cross-sectional and longitudinal phase.

The cross-sectional phase was conducted through yearly surveys of 2 wk duration. The survey tried to assess the demographic characteristics of type 1 and type 2 patients with diabetes mellitus, along with their therapeutic management in the current medical practice. The longitudinal phase was conducted in the first two out of five waves, and consisted of a 9-mo follow-up period focused on different parameters. The sixth Wave of the study did not include a longitudinal phase.

The number of participating physicians and their profile was decided upon on a country basis, where the number of physicians chosen depended on the patient sample size, which was individualized in each country. Since each physician was asked to enroll 10 patients with diabetes mellitus, the number of physicians was determined by dividing the number of patients by 10. Physicians were selected randomly and were asked to recruit, during a 2-wk period, the first 10 patients with type 2 diabetes presenting to their clinics who were older than 18 years of age, as well as the first 5 patients with type 1 diabetes. In Lebanon, 80 sites were selected and the plan was to recruit 1,000 patients. A total of 77 physicians and 1,159 patients were included in 2011, and 60 physicians and 600 adult male or female patients were included into the sixth Wave in the year 2013. A signed written informed consent was obtained from all participating patients before the application of any study-related procedures. These consent forms were available in English as well as in Arabic for those participants who did not understand the English language. Ethics committee approval was obtained from participating centers where such committees are in place.

Exclusion criteria included concomitant enrollment in any other study, gestational diabetes, and cancer of the pancreas. Finally, 596 were included in the analysis population. Among these patients, one was a type 1 diabetic patient and the rest were type 2.

Data were collected on the demographic characteristics of the patients, their relevant medical history, the treatments prescribed for their diabetes, whether oral, insulin or others, the frequency of screening and testing for any observed diabetes complications, and cardiovascular risk factors. Data on metabolic control were also evaluated. The IMPDS 2006 and 2011 data were already published in separate papers[11,12].

The SAP (version of 6 November 2014) used for this analysis aimed at describing the cross-sectional analysis of the sixth year (Wave 2013-2014). Proportions are reported as percentages of completely included populations, and means are reported as continuous variables ± standard deviations.

RESULTS

Physician characteristics

In Lebanon, in Wave 2013-2014 of the cross-sectional IDMPS study, the total number of physicians enrolling at least 1 patient into the study was 60. Among these physicians, 47 were specialized and 13 non-specialized. Forty-three (71.7% were males) had a mean age of 52.18 ± 9.63 years. Forty-seven (78.3%) were endocrinologists and the remainder were either internists, general practitioners or cardiologists. The median length of duration of medical practice was 21.42 ± 9.47. The mean total number of patients with diabetes seen per day among the included physicians was 16 ± 12.

Patient characteristics

Six hundred patients with diabetes mellitus were recruited. Five hundred and ninety-six patients met the eligibility criteria for analysis. One patient with type 1 diabetes (representing 0.1% of all type 1 diabetes mellitus patients), and 595 with type 2

diabetes (representing 10.9% of all type 2 diabetes mellitus patients) were recruited. The analyses were done on patients with type 2 diabetes mellitus due to having only 1 patient with type 1 diabetes mellitus. Demographic characteristics of the type 2 diabetes patients are included in Table 1.

The average population age was 59 years, with a higher percentage of the male population included. The average BMI of inclusion was 30, which is in the obese range, and this was higher than the one reported in 2011. As for female participants, 23.8 had a BMI ≥ 30, and 47.9% had a BMI between 25-29. As for male participants, 25% had a BMI ≥ 30, and 50% had a BMI between 25-29. The majority of patients were on oral glucose lowering therapy. In addition, the mean time of diabetes diagnosis was 8.8 years. Around 75% had a positive family history of diabetes. Around 70% of patients had dyslipidemia, the majority of which were treated, but metabolic control was not achieved, as only 40% of treated patients had low-density lipoprotein (LDL) less than 100 mg/dL, and 44% had Triglyceride levels less than 150 mg/dL. In Table 2, data from 2013 was compared to that of 2011.

Glycemic control

Concerning patient management, the patient with type 1 diabetes mellitus was maintained on insulin therapy. As for the patients with type 2 diabetes, the majority were on oral anti-diabetic medications. The percentage of patients on insulin therapy was 3.7% in year 2013. Patients included had on average 8 years of diabetes. The percentage who had diabetes diagnosed more than 20 years ago was 6.4% and 70.1% of patients had health insurance (69% was public insurance, 19% was private insurance, and the rest had both forms of insurance).

The number of patients who had a glucose meter was found to be 439 (75.3%), where 406 (94.4%) did self-monitoring with their glucose meter. Regarding the glycemic control of the studied population, the mean fasting serum glucose was 159.42 mg/dL and the mean HbA1c level was 7.98, with around 30% achieving an HbA1c target of less than 7%. Eighty-eight (15.4%) patients experienced one hypoglycemic episode, among which 61.9% were on insulin treatment and 28.8% on combined oral hypoglycemic agents and insulin. As for severe hypoglycemia, it was more clearly found in the insulin-treated group, as expected. Out of all participants, 87.4% had metabolic syndrome based on the IDF definition. Among the included patients with diabetes, 318 (56.5%) mentioned that they do follow a healthy diet and exercise plan.

Screening for diabetes complications

The screening for diabetes complications, both micro-vascular and macro-vascular, by healthcare professionals appears to be improving. Patients were questioned about being screened at least once for diabetic complications during the last year before recruitment.

Concerning microvascular complications, it was found that in 2013, 65.7% of patients with type 2 diabetes were screened for retinopathy, 82.5% for nephropathy and 53.9% for peripheral neuropathy.

Foot examination screening occurred in 63.9%. Screening for cardiovascular disease occurred in 76.9% of patients. Screening for hyperlipidemia occurred in 95%, and screening for blood pressure control was in 86.1% (Table 3). When all late diabetes complications were combined, 38.6% of patients were found to have at least one complication (Table 4).

Blood pressure and lipid control

Three hundreds and fifty-seven (60.3%) patients reported having hypertension, among which 98% were being treated for it. The mean systolic blood pressure was 130, and the mean diastolic blood pressure was 77.9. Around 40% of patients had a systolic blood pressure of less than 130, and an equal number had a diastolic blood pressure less than 80. Concerning antihypertensive treatment, 33.3% of patients were treated with Angiotensin Converting Enzyme Inhibitors (ACEI) and 50% were on angiotensin II receptor blockers (ARB). The use of anti-platelets therapy was 42.4% in the year 2013. In addition, many patients (52.7%) were found to be smokers.

Dyslipidemia was found to be prevalent among our patients with diabetes mellitus (68.4%), and 94.8% were being treated (Table 5). Concerning the patients' fasting lipid profile, 39.2% of patients had an LDL < 100 mg/dL and their mean fasting LDL was 125.45 ± 135.12 mg/dL. In contrast, 44% of the type 2 diabetic population had triglyceride levels below 150 mg/dL in 2013, with a mean TG level of 178.53 ± 104.12. In addition, 86.5% of treated patients were on statin therapy.

The Lebanese population of patients with type 2 diabetes has an increase in the mean BMI over the years, where the average BMI of inclusion was 30, which is in the obese range. This was higher than that reported in the years 2006 and 2011, when it

Table 1 Demographic characteristics of patients with diabetes mellitus

Characteristics of type 2 diabetes patients	
Age, mean ± SD	59.37 ± 10.85
Female, *n* (%)	307 (51.6)
Body mass index in kg/m^2, mean ± SD	30.13 ± 5.47
Waist circumference in cm, mean ± SD	100.25 ± 13.14
Residence, *n* (%)	
Urban	375 (63.0)
Rural	126 (21.2)
Sub-urban	94 (15.8)
Health insurance	
Yes	417 (70.1)
No	178 (29.9)
Time since diabetes diagnosis in yr, mean ± SD	8.88 ± 7.19
Family history of diabetes, *n* (%)	
Yes	436 (76)
No	138 (24)
Time since diabetes diagnosis in yr, *n* (%)	
≤ 1	85 (14.3)
1-5	162 (27.3)
5-10	137 (23.1)
10-20	171 (28.8)
> 20	38 (6.4)
Treatment of diabetes	
Diet and exercise alone	10 (1.7)
OGLD	421 (70.7)
Insulin treatment	22 (3.7)
OGLD treatment + insulin treatment	124 (20.8)
Other (No OGLD - no insulin - no diet)	18 (3)
Level of education, *n* (%)	
Illiterate	54 (9.1)
Primary	207 (34.9)
Secondary	228 (38.4)
University/higher education	104 (17.5)
Health insurance coverage, *n* (%)	
None	178 (29.9)
Public	288 (69.1)
Private	80 (19.2)
Public and private	49 (11.8)
Smoking habit, *n* (%)	
Never	150 (25.2)
Former	131 (22.0)
Current	314 (52.8)
Hypertension, *n* (%) [95%CI]	356 (60.2) [56.2%; 64.2%]
Patient receiving anti-platelet therapy, *n* (%)	236 (42.4)
Dyslipidemia, *n* (%) [95%CI]	401 (68.3) [64.4%; 72.1%]

OGLD: Oral glucose lowering drugs.

was 29.04 and 28.92, respectively. This could be due to a lack of compliance of patients to proper diet instructions, or the lack of sufficient education by physicians regarding the importance of losing weight and physical activity. BMI is known to be strongly and independently associated with type 2 diabetes mellitus, and this has been confirmed in Lebanese patients as well[4,15].

Among the recruited cohort of patients with type 2 Diabetes in 2013, the mean

Table 2 Baseline characteristics of patients with diabetes mellitus in 2011 and 2013

	IDMPS 2013	IDMPS 2011
Total patients recruited	596	1157
Age in yr	59.37	56.42
Male/female, *n*/*n*	289/307	588/569
BMI, kg/m^2	30.13	28.92
BP control		
Mean BP	130.03/77.89	130.8/79.7
SBP < 130, %	40.2	43.7
DBP < 80, %	39.8	33
HTN treatment		
ACEI, %	33.3	36.2
ARB, %	50	50.1
Antiplatelet therapy, %	42.4	45.7
Dyslipidemia and management		
Diagnosed with dyslipidemia, %	68.3	68
LDL < 100 mg/dL, %	39.2	39.3
HDL ≥ 40 mg/dL, %	68.5	62.7
TG < 150 mg/dL, %	44.4	39
Statin therapy, %	86.5	82.7
Glycemic control		
Mean HbA1c	7.98	7.79
HbA1c < 7%, %	31.4	36.1

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HTN: Hypertension; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blockers; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; HbA1c: Glycosylated hemoglobin.

duration of diabetes was 8.88 (± 7.19) years, which was similar to that found in 2011, which was 8.11 (± 7.23) years. As for the long-standing history of diabetes, being defined as more than 20 years, it was found to be 6.4% in the year 2013, compared to 30.3% (around one third) in 2011.

In addition, it was found that 30% were able to achieve an HbA1c target of less 7%, and this stresses the need for having more proper follow-ups of patients, as well as the need to follow international guidelines on diabetes[9,10]. This would ensure that a higher percentage of patients have better control of their diabetes mellitus and are below the target required for HbA1c levels.

In our study, we also noted that insulin use as the sole treatment strategy has declined from 7.5% in 2006 to 3.7% in year 2013, and thus more patients were found to be on a combination of oral hypoglycemic agents and insulin. This could be interpreted by the fact that a lesser number of included patients in year 2013 had long-standing diabetes mellitus of more than 20 years duration. The other explanation could also be partly related to the vast new hypoglycemic agents, which were introduced to the Lebanese market during that period of time, namely the incretins and SGLT 2 inhibitor family.

Concerning the screening for microvascular complications, 65.7% of patients in 2013 with type 2 diabetes were screened for retinopathy, while this was 68.5% in 2011 and 53.2% in 2006. As for diabetic nephropathy and peripheral neuropathy, the screening proportions were 82.5% and 53.9%, respectively (as compared to being 63.4% and 47.9% in year 2006). Foot examination screening occurred in 63.9%. Screening for cardiovascular disease occurred in 76.9% of patients, which was 77.1% in the year 2011. It was noted that there were improved screening rates for diabetes complications in 2013 when compared to the year 2006, which probably shows that there is currently an increased awareness by physicians of the importance of screening to prevent late complications and poorer outcomes. However, it is important to note that screening methods have not increased when compared to the year 2011. However, upon checking other studies, it was noted that there was a worldwide failure to achieve glycemic targets. In the multinational, observational study that included 66,726 people with type 2 diabetes, who were enrolled from 28 countries across four continents (Asia, Africa, Europe and South America), 53.5% had

Table 3 Screening of diabetes-related complications in patients with diabetes mellitus

Screening for any diabetes-related complication, *n* (%)	
Yes	553 (97.9)
No	12 (2.1)
Screening for cardiovascular disease	
At least one time during the past year	376 (76.9)
Never	113 (23.1)
Eye screening	
At least one time during the past year	295 (65.7)
Never	154 (34.3)
Number of eye screening, mean (SD)	1.20 (0.57)
Screening for nerve damage	
At least one time during the past year	232 (53.8)
Never	199 (46.2)
Number of screening for nerve damage, mean ± SD	1.75 ± 1.01
Screening for kidney damage	
At least one time during the past year	425 (82.5)
Never	90 (17.5)
Number of screening for kidney damage, mean ± SD	1.87 ± 1.02
Screening for foot examination	
At least one time during the past year	297 (63.9)
Never	168 (36.1)
Number of screening for foot examination, mean ± SD	1.90 ± 1.08
Screening for blood lipid control	
At least one time during the past year	496 (94.8)
Never	27 (5.2)
Number of screening for blood lipid control, mean ± SD	2.06 ± 1.04
Screening for blood pressure control *n* (%)	
At least one time during the past year	286 (86.1)
Never	46 (13.9)
Number of screening for blood pressure control, mean ± SD	2.57 ± 1.17

microvascular complications and 27.2% had macrovascular complications[16]. Similarly, in another study in India, a high prevalence of complications among patients with diabetes mellitus was reported, with 60% having neuropathies, 20% having cataracts, 15.4% having retinopathies, 32.3% having coronary heart disease, 11.5% having PVD, and 6.9% having a history of cerebrovascular accidents[17].

With regards to hypertension, a large percentage (60%) were diagnosed with hypertension, the majority of which were treated. However, a small percentage had a systolic blood pressure of less than 130, and an equal number had a diastolic blood pressure less than 80. This again shows the need to have more proper control of hypertension in patients with diabetes mellitus. When comparing our results to another study, it was found that the frequency of WHO-defined hypertension was high in the non-insulin-dependent patients who were older than 55 years, with a percentage of 43% for males and 52% for females, in a sample of 5,842 patients attending ten diabetic clinics in the London area[18]. The prevalence of hypertension was also looked at amongst 450 persons with diabetes mellitus in Benin city, and a prevalence rate of 54.2% was found[19]. In addition, a study in Jordan was conducted, and the prevalence of hypertension defined as a BP > 130/80 or on medication for high blood pressure among type 2 diabetes patients was 72.4% (70.9% of males and 73.9% of females)[20].

Concerning antihypertensive treatment, less patients were treated with ACEI (33.3%), as compared to an earlier report showing 46.2% usage in 2006 and 36.2% in 2011, respectively. As for ARB, 50% were on this medication, and this was the same in the year 2011. The pattern of antihypertensive treatment among type 2 diabetes patients were looked at in 9,975 patients obtained from an outpatient medical center of the Department of Veterans Affairs, and it was found that over 60% of patients were receiving ACEI or ARB[21]. Another study was conducted in the rural

Table 4 Reported diabetes-related complications for patients with type 2 diabetes mellitus

Reported diabetes-related complications	*n* (%)
Any diabetes-related complication	264 (45.7)
Microvascular complications	
At least one microvascular complication	223 (38.6)
Retinopathy	77 (13.3)
Sensory neuropathy: abnormal sensation in distal limbs	125 (21.6)
Microalbuminuria: lab test	130 (22.5)
Proteinuria: dip stick	20 (3.5)
Dialysis	1 (0.2)
Amputation: below knee or above knee	2 (0.3)
Foot ulcer: active or past history	13 (2.2)
Macrovascular complications	
At least one macrovascular complication	122 (21.1)
Angina	31 (5.4)
Myocardial infarction/acute coronary syndrome	38 (6.6)
Heart failure	11 (1.9)
Stroke with partial recovery	4 (0.7)
Stroke with full recovery	8 (1.4)
Peripheral vascular disease	59 (10.2)
History of revascularization: *e.g.*, PTCA, CABG	41 (7.1)
Other complications	20 (3.5)

southeastern Australia, including a total of 449 patients with hypertension and diabetes, and 39% of those patients were taking ACEI, while another 39% were taking ARB[22].

Despite clinical practice guidelines recommending the use of antiplatelet therapy in patients with diabetes, the use of anti-platelets therapy in our study was shown to have decreased from 2006 to 2013, from 60.6% to 42.4% in the year 2013. In another study, in a cohort of primary care patients with type 1 or type 2 diabetes, which was part of a larger project called the Vermont Diabetes Information System, the prevalence of antiplatelet use was found to be 54%[23].

The same applies to lipid control, where 68% of our patients had dyslipidemia, and around 40% only had LDL < 100 mg/dL despite having 86.5% of patients on statin therapy. This shows that patients need more proper care, and physicians need to follow diabetes guidelines so as to have a larger number of patients who have appropriate treatment of their diabetes, hypertension and lipid control. Our results are better than another study done, which showed that diabetic dyslipidemia participants were being treated less often with lipid-lowering therapy[24].

Conclusion

In conclusion, the Wave 6 results of the IDMPS study does reveal a promising improvement in the management of diabetes mellitus; however, not enough patients are actually achieving the target glycemic control. Thus, a national effort is needed in order to have a more appropriate control of diabetes, hypertension and lipids. Screening of diabetes-related complications is improving, but at a slow rate. Treating physicians are becoming more aware of the necessity of screening for complications, but despite all their efforts, the glycemic and metabolic control of the Lebanese type 2 diabetes population is still not sufficient. There should be more emphasis on educating the population about the importance of lifestyle modifications and obesity control, which will eventually help to improve type 2 diabetic patient outcomes.

Table 5 Dyslipidemia among patients with diabetes mellitus, *n* (%)

Dyslipidemia among patients with type 2 diabetes mellitus	
Patient diagnosed with dyslipidemia	402 (68.4)
Patient treated for lipids	380 (94.8)
Current treatment	
Statins	329 (86.6)
Fibrates	92 (24.2)
Nicotinic acid	0
Other treatment for dyslipidemia	3 (0.8)

ARTICLE HIGHLIGHTS

Research background

Diabetes mellitus is a common worldwide problem associated with significant morbidities and mortalities. This paper assesses the therapeutic management and control of patients with diabetes mellitus in the current medical practice in the Lebanese population. It identifies the proportion of subjects with target glycosylated hemoglobin (HbA1c) in compliance with the international recommendations' guidelines, and the factors that would be predictive of reaching target HbA1c. It also identifies the percentage of patients with diabetes who are screened for complications of diabetes. Furthermore, the percentage of patients who have hypertension or dyslipidemia, or who are taking antiplatelet treatment, is also tackled. In addition, the assessment of the health economic impact of patients with type 2 diabetes and its complications is tackled.

Research motivation

The results discuss our findings in relation to the treatment strategies and goals recommended by the American Diabetes Association and the European Association for the Study of Diabetes. This will also help physicians with better management and follow-up practices for patients with diabetes mellitus, and underscores the need for proper screening of complications and other risk factors commonly associated with diabetes mellitus.

Research objectives

In this paper, data from Wave 2013-2014 of the International Diabetes Management Practices Study (IDMPS) were retrieved and analyzed. Endpoints included the proportion of subjects with target HbA1c in compliance with the international recommendations' guidelines, the frequency of screening for diabetes complications and its risk factors, and the assessment of the health economic impact of type 2 diabetes and its complications.

Research methods

The IDMPS is an international study, observational in nature, conducted in multiple centers in non-Western countries, and included patients with diabetes mellitus who were randomly selected from a representative pool of diabetic patients. It involved six waves, beginning in 2006 and ending in 2014, with each wave being conducted yearly, and consisting of a cross-sectional and longitudinal phase. The cross-sectional phase was conducted through yearly surveys of 2 wk duration, and tried to assess the demographic characteristics of patients with diabetes mellitus, along with their therapeutic management in the current medical practice. The sixth Wave of the study did not include a longitudinal phase. A total of 60 physicians and 600 adult male or female patients were included into the sixth Wave in the year 2013. A signed written informed consent was obtained from all the participating patients before the application of any study-related procedures. Ethics committee approval was obtained from participating centers where such committees are in place. The SAP (version of 6 November 2014) used for this analysis aimed at describing the cross-sectional analysis of the sixth year (Wave 2013-2014). Proportions are reported as percentages of all the included populations, and means are reported as continuous variables ± standard deviations.

Research results

Five hundred and ninety-five patients with type 2 diabetes were included in Wave 6, and only a single patient with type one diabetes mellitus was included. The average age was around 60 years, with a mean BMI of 30. The mean fasting serum glucose was 159.42 mg/dL and mean HbA1c level was 7.98, with around 30% achieving an HbA1c target of less than 7%. More patients were on oral anti-diabetic medications, probably related to the recent introduction of new oral medications. Screening of diabetic complications has improved over the years. A large percentage of patients were diagnosed with hypertension and dyslipidemia, the majority of which were treated, but a small percentage controlled.

Research conclusions

The results of the IDMPS study Wave 6 shows that there is a promising improvement in the

management of diabetes mellitus; however, it is still obvious that there are not enough patients achieving the target glycemic control. There is still not sufficient screening for diabetes-related complications and its risk factors. This is in concordance with the hypothesis we had prior to study initiation.

Research perspectives

This research offers new perspectives concerning the need for more awareness campaigns to both physicians and patients with diabetes mellitus. Thus, a national effort is needed in order to have a more appropriate control of diabetes, hypertension and lipids. Screening of diabetes-related complications is improving, but at a slow rate and not significantly compared to previous years. There should be more emphasis on educating the population about the importance of lifestyle modifications and obesity control, which will eventually help to improve type 2 diabetic patient outcomes.

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EVIDENCE-BASED MEDICINE

Are serum leptin levels predicted by lipoproteins, vitamin D and body composition?

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Abstract

BACKGROUND

Both obesity and vitamin D deficiency are important health issues in Pakistan. The connection between body composition, Vitamin D and leptin in young adults is important to be studied as body composition may affect bone health and therefore the possibility of osteoporosis in later life. Few studies have attempted to investigate the effect of body composition and leptin with vitamin D in adolescence.

AIM

To investigate the association of serum leptin with body composition, lipids and 25-hydroxyvitamin D (25OHD) in adults.

METHODS

This cross-sectional study was conducted on 167 apparently healthy adults. Demographics were recorded, bioelectrical impedance analysis was performed and clinical history noted. Serum leptin was measured using DIA source kit on ELISA and total 25OHD was measured on ADVIA-Centaur; Siemens. Total cholesterol and high density lipoprotein cholesterol were quantified using Enzymatic Endpoint Method and Cholesterol Oxidase-Phenol Aminophenazone method respectively. Biochemical analysis was done in the Departments of Pathology and Laboratory Medicine and Biological and Biomedical Sciences, Aga Khan University Hospital Karachi Pakistan.

RESULTS

Median age of the group (n = 167) was 20 years (IQR 27-20); 55.7% were females.

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Majority (89.2%, n = 149) of the study group was 25OHD deficient, 6% (n = 10) had insufficient serum 25OHD levels and 4.8% (n = 8) had sufficient D levels. Females, had higher median leptin levels [2.71 (IQR 4.76-1.66 ng/mL)] compared to their counterparts [1.3 (3.60-0.54 ng/mL), P < 0.01]. Multiple regression analysis suggested that basal metabolic rate, muscle mass, body fat percent, bone mass and serum 25OHD were the most contributing factors to serum leptin levels. Bone mass and serum 25OHD in fact bore a negative correlation with leptin.

CONCLUSION
The results indicate that basal metabolic rate, muscle mass, body fat percent, bone mass and serum 25OHD have an impact on serum leptin. Being a cross sectional study causal relationship between leptin and other variables could not be determined.

Key words: Leptin; Vitamin D; Obesity; Vitamin D deficiency; Body fat

Core tip: The paper explored variables like anthropometric measurements, body composition, vitamin D and lipoproteins as predictors for serum leptin levels among representative population of healthy adults in Pakistan. The cross-sectional nature of this study could not elucidate causal relationships. However, it outlines important interplay between circulating leptin, vitamin D and body composition. The results indicate that basal metabolic rate, muscle mass, body fat percent, bone mass and serum vitamin D have an impact on serum leptin.

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INTRODUCTION

Quite a few cross-sectional studies have explored leptin and obesity in relation to Vitamin D deficiency (VDD) but the findings is inconsistent and conflicting[1-4]. The limited available literature differs considerably in terms of study design, subjects studied and results reported, making it challenging to infer. The cause-effect relationship between leptin, VDD and obesity remains unclear. The link between vitamin D and obesity has been put forward by some genetic and secondary lines of evidences[5-7]. Secondary factors common to both obesity and VDD are environmental aspects like dietary, racial, topographical, seasonal, and environmental pollution[8-10]. Genetic studies have shown to link molecular variations of Vitamin D metabolism with obesity[11-13]. The hereditary risk factors include polycystic ovary disease, cytochrome P450, locus 20q13, vitamin D-binding protein gene polymorphisms, and *aP2* gene. The VDR polymorphisms were described to be linked to adiposity phenotypes[14,15].

Given the potential for positive associations of VDD and leptin concentration with obesity and the development of cardiovascular disease, the identification of modifiable lifestyle factors associated with leptin levels is vitally important to prevent obesity and its associated complications[16]. Additionally, the connection between body composition, especially fat content in the body, and Vitamin D and leptin in young adults is clinically vital because management that modify body weight may affect bone health and therefore the possibility of osteoporosis in later life. Few studies have attempted to investigate the effect of body composition and leptin with vitamin D in adolescence[17,18]. This study was conducted to analyze serum leptin concentrations in samples from adult volunteers and correlate it with body composition parameters, difference in gender, 25-hydroxy vitamin D (25OHD) and lipids.

MATERIALS AND METHODS

Study design and study group

This cross sectional analysis was done from June 2014 till January 2016, in the Section of Clinical Chemistry, Department of Pathology and Laboratory Medicine and Department of Biological and Biomedical Sciences, Aga Khan University Hospital Karachi Pakistan. Apparently healthy adult volunteers were invited to join in the research once informed consent was taken. Approval from the Aga Khan University Ethical Review Committee was taken for conducting this study (ERC number: 2810-Pat-ERC-13). A 4-d phlebotomy camp was set up in the Multidisciplinary Laboratory on the University campus for collection of blood samples. Subjects were excluded if they reported having had: intramuscular supplementation of Vitamin D in the last 6 mo, remarkable changes in weight or diet in the last 6 mo, any disease that may affect their Vitamin D levels or any known metabolic disorder. Subjects taking small dose of oral Vitamin D supplements, for example such that may be contained in a daily multivitamin pill (400 IU) since such a low amount would not significantly change serum 25OHD levels, were allowed to participate[19].

Clinical history, anthropometric measurements and phlebotomy

An interviewer-administered history form tailored for the adult Pakistani urban population[20], was used to assess the clinical history and health status of the study group. Waist circumference was measured in cm. Each subject's weight (kg) and height (m) were recorded, and the resultant body mass index (BMI) was calculated and reported in kg/m^2. BMI values were categorized as per the recommended reference ranges for the Pakistani population[21]. A bioelectrical impedance analyzer (BIA) by Tanita was used to assess body composition variables of the study group. BIA is a validated method of estimating adiposity in both clinical and non-clinical settings[22]. BIA measurements included total body fat percentage (reported as %), total body water percentage (reported as %), total muscle mass (reported in kg), basal metabolic rate (reported in kcal) and total bone mass (reported in kg). International body fat reference ranges for young adults were used to group subjects.

After informed consent blood was drawn in gel separation tubes and centrifuged at 3500 rpm for 5 min for separation of serum. Separated serum was transferred to aliquots, labeled with the participant's serial number and immediately stored at -30°C.

A BIA was used to assess body composition variables of the study group. BIA is a validated method of estimating adiposity in both clinical and non-clinical settings[22]. BIA measurements included total body fat percentage, total body water percentage, total muscle mass, basal metabolic rate and metabolic age, total bone mass and visceral fat mass. International body fat reference ranges for young adults were used to group subjects.

Biochemical analysis and interpretation

Leptin was measured using manual ELISA on a kit from DIA source (Belgium). The microtiter wells were coated with a monoclonal anti-leptin antibody. 25OHD was quantified by chemiluminescence on ADVIA Centaur Immunoassay System (Siemens AG, Munich, Germany) in batch. The measuring range of the assay was 3.7-150 ng/mL. Total cholesterol was measured using an enzymatic endpoint method, while cholesterol oxidase-phenol aminophenazone method was used for analysis of high density lipoprotein (HDL) cholesterol by using kits from Randox Laboratories, United Kingdom on spectrophotometer. Non HDL was calculated by subtracting HDL from total cholesterol. To validate the biochemical results high and low levels of quality control material for leptin, 25OHD, cholesterol and HDL were run with the batches. Classification of VDD was based on the circulating 25OHD concentrations of less than 20 ng/mL. Levels between 20-30 ng/mL as insufficiency and > 30 ng/mL as sufficient D levels. Serum leptin was interpreted taking both BMI and gender into account.

Statistical analysis

All Statistical analysis was done on R-Software (R Version 3.5.3) and Statistical Package for Social Sciences (Version 22, SPSS Inc. Chicago, IL.). All parametric variables were reported as mean ± SD and non-parametric as median with interquartile ranges 75th-25th. Differences between two groups of parametric variables were evaluated using independent samples *t*-test. To compare median values between two groups Mann Whitney *U* test was applied. Serum leptin and 25OHD were not normally distributed and hence were log transformed before correlation was conducted. As an initial step, we explored Pearson correlational relationships and applied Chi-square for categorical data between the measured independent variables taking serum leptin as dependent variable. Univariate analysis was conducted and variables that had significant association with leptin in univariate analysis at $P < 0.2$

were entered in multivariable analysis. Multivariate regression analyses were conducted for the dependent variable (serum leptin) and independent variables [BMI, basal metabolic rate (BMR), muscle mass, body water %, body fat %, bone mass, waist circumference, log 25OHD, male gender]. For working out the magnitude of associations between independent-dependent variables, beta weight of the variables was calculated. All tests were two-tailed, and the level of significance was set to *P*-value less than 0.05 as significant and < 0.01 was considered greatly significant.

RESULTS

Description of demographics and body composition of study group

A total of 167 subjects were enrolled; there was a near equal gender distribution with Female: Male 93:74. No statistically significant difference for age was found between the two genders. None of the subjects studied had any clinical signs of disease associated with obesity and were not on any medications. Of the total seven were cigarette smokers (4.1%); 2 smokers were females and the rest were males. Characteristics of the study population are summarized in Table 1.

No statistically significant difference in BMI between males and females was noted however, the male adolescents had significantly higher body height and weight than their female counterparts ($P < 0.001$). According to the South-Asian Classification of weight status, 14.4% ($n = 24$) of the study-subjects were categorized as underweight (less than 18.5 kg/m^2), 40.1% ($n = 67$) as normal (from 18.5 to 22.9 kg/m^2), 22.2% ($n = 37$) as overweight (from 23 to 25 kg/m^2) and 23.4% ($n = 39$) as obese (greater than 25 kg/m^2).

Taking age and gender into account study subjects were additionally stratified according to body fat percent as under fat, healthy, over fat and obese. Upon stratification according to body fat percent 14.4 % ($n = 24$) were obese while 12.6% ($n = 21$) were overweight. Body fat % was significantly higher amongst subjects who were overweight and obese as per BMI [mean body fat %: 27.5 (7.5)] as compared to non-obese [mean body fat %: 17.5 (6.8)] as depicted in Table 2. Percent of body water in study subjects was ideal (*i.e.*, 45%-60% in females and between 50%-65% in males) in 80% subjects ($n = 142$), low in 6% ($n = 10$) and excessive in 9% ($n = 15$).

Biochemical specifics of study subjects

A Shapiro Wilk test ($P < 0.05$) and visual scrutiny of 25OHD and leptin histograms, Q-Q plots and box plots showed that both analytes were not normally distributed, with a skewness of 1.8 (S.E 0.18) and 3.5 (S.E 0.18) respectively and kurtosis of 5.9 (S.E 0.37) and 17.4 (S.E 0.37) respectively. Majority (89.2%, $n = 149$) of the study group was 25OHD deficient, 6% ($n = 10$) had insufficient serum 25OHD levels and 4.8% ($n = 8$) had sufficient D levels. Of a total of 167 sera analyzed, the lowermost and uppermost serum leptin levels noted were 0.02 and 45.3 ng/mL, respectively. Females had higher median leptin levels [2.71 (IQR: 4.76-1.66 ng/mL)] compared to males [1.3 (3.60-0.54 ng/mL), $P < 0.01$]. Overall 17 (10.1%) study subjects had raised serum leptin levels with 88.2% ($n = 15$) of these subjects being Vitamin D deficient. However, 89.3% ($n = 134$) of the subjects with normal serum leptin were also deficient in 25OHD.

Determinants of serum leptin

The Table 2 describes the relevant Pearson correlation coefficients and their degrees of significance between leptin and other variables in the total study population and in both genders separately. A greatly significant, moderate positive linear relationship was seen between log of leptin and BMI, waist circumference and also with total body fat percent in females ($P < 0.01$). While a greatly significant negative association was prominent between log of serum leptin and total water percent and basic metabolic rate in the females ($P < 0.01$). In males log leptin exhibited positive relation with BMI ($P < 0.05$), waist circumference ($P < 0.05$) and body fat percent ($P < 0.01$) and inverse correlation with total water percent, muscle mass and log 25OHD ($P < 0.01$). Variables that had significant association with leptin in univariate analysis at $P < 0.2$ were entered in multivariable analysis.

Multiple regression analysis displayed that BMR, muscle and bone mass, body fat percent, 25OHD and gender were the utmost contributing factors to serum leptin levels. Bone and muscle mass and serum 25OHD bore an inverse relation with serum leptin. The value of R square and adjusted R square was 0.387 and 0.352 respectively specifying strong association between various independent and dependent variables. This showed a positive relationship of 38.7% between independent and dependent variable (leptin). Corrected R square indicated the fit of the model more closely in population. Table 3 summarizes the results of multivariate regression analysis. It

Table 1 Demographics, body composition and biochemical parameters and comparison amongst genders and obese *vs* non obese

Description	Overall	Males	Females	*P* value	Overweight and obese (BMI > 23 kg/m²)	Non obese (BMI < 23 kg/m²)	*P* value
n	167	74	93		76 (50% Females)	91 (60.4% Females)	
Anthropometric parameters							
Median age (IQR) in yr	20 (27-20)	21(29-20)	20(23-20)	0.136	21 (35.5-20)	20 (21-20)	< 0.01
Mean height (SD) in cm	168 (9.2)	172 (8.2)	164.8 (8.7)	< 0.01	167.9 (9.7)	168.1 (8.8)	0.837
Mean weight (SD) in kg	65.0 (4.4)	70.2 (14.9)	60.9 (12.6)	< 0.01	75.1 (14.1)	56.6 (7.7)	< 0.01
Mean BMI (SD) in kg/m^2	23 (4.6)	23.7 (5.1)	23.7 (5.1)	0.056	26.6 (4.3)	19.9 (1.8)	< 0.01
Mean waist circumference (SD) in cm	79.1 (12.8)	83.3 (13.3)	75.7 (11.3)	< 0.01	86.9 (12.4)	72.5 (8.8)	< 0.01
Body composition							
Mean total body fat % (SD)	22.1 (8.7)	19.7 (9.0)	23.9 (8.0)	< 0.01	27.5 (7.5)	17.5 (6.8)	< 0.01
Under fat *n* (%)	44 (26.3)	5 (6.8)	39 (41.9)	< 0.01	3 (3.9)	41 (45)	< 0.01
Healthy *n* (%)	78 (46.7)	38 (51.4)	40 (43)	< 0.01	33 (43.4)	45 (49.4)	< 0.01
Over fat *n* (%)	21 (12.6)	11 (14.9)	10 (10.8)	< 0.01	19 (25)	2 (2.1)	< 0.01
Obese *n* (%)	24 (14.4)	20 (27)	4 (4.3)	< 0.01	21 (27.6)	3 (3.2)	< 0.01
Mean total body water %	55.7 (6.1)	57.8 (6.3)	54.1 (5.4)	< 0.01	52.3 (4.9)	58.6 (5.5)	0.255
Ideal body water *n* (%)	142 (85)	61 (82.4)	81 (87.1)	0.235	68 (89.4%)	74 (81.3%)	< 0.01
Mean muscle mass (SD) in kg	45.7 (7.9)	50.2 (8.4)	42 (5.1)	< 0.01	46.3 (8.7)	45.1 (7.2)	0.357
Median BMR (IQR) in kcal	1501 (1750-1336)	1732 (1875-1551)	1377 (1525-1300)	< 0.01	1690 (1892.5-1421.5)	1417 (1612-1308)	< 0.01
Median bone mass (IQR) in kg	2.5 (3-2.1)	2.9 (3.2-2.6)	2.2 (2.4-2)	< 0.01	2.9 (3.2-2.3)	2.2 (2.8-2.0)	< 0.01
Healthy bone mass *n* (%)	71 (42.5)	31 (41.9)	40 (43)	0.884	36 (47.3%)	35 (38.4%)	0.273
Biochemical parameters							
Median leptin (ng/mL)	2.2 (4.5-1.0)	1.3 (3.60-0.54)	2.71 (4.76-1.66)	< 0.01	3.0 (5.8-1.5)	1.7 (3.4- -0.7)	< 0.01
Elevated serum leptin *n* (%)	17 (10.2)	7 (9.5)	10 (10.8)	0.784	9 (11.8%)	8 (8.8%)	0.61
Median 25OHD (IQR) in ng/mL	12.1 (16.1-7.7)	12.5 (16-8.5)	11.5 (16.6-7.5)	0.877	12.1 (16.8-8.5)	12 (15.9-7.1)	0.479
25OHD status: Deficiency *n* (%)	149 (89.2)	69 (93.2)	80 (86)		67 (88.1%)	82 (90.1%)	
25OHD status: Insufficiency *n* (%)	10 (6)	5 (6.8)	5 (5.4)	0.03	4 (5.2%)	6 (6.5%)	0.585
Sufficiency *n* (%)	8 (4.8)	-	8 (8.6)		5 (6.5%)	3 (3.2%)	
Mean total cholesterol (SD) in mg/dL	175.8 (46.3)	172 (49.4)	178.8 (43.7)	0.345	180.8 (48.6)	171 ± 44	0.199
Mean HDL (SD) in mg/dL	41.1 (9.6)	40.4 (10)	41.6 (9.2)	0.44	40.5 (9.4)	41.540.5 ± 9.49.7	0.498
Mean non-HDL (SD) in mg/dL	134.7 (47.2)	131.5 (52.4)	137.2 (42.8)	0.446	14040.5 (9.450.1)	13040.5 ± 9.444.4	0.163

Parametric variables are reported as mean ± SD and non-parametric as median (interquartile ranges 75th-25th). Coefficients (*r*) and *P* values are calculated using Pearson's correlation analysis. *P*-value less than 0.05 was considered as significant and < 0.001 as highly significant. BMI: Body mass index; BMR: Basal metabolic rate; 25OHD: 25-hydroxy vitamin D; HDL: High density lipoprotein.

Table 2 Correlation of metabolic and biochemical factors with serum log leptin according to gender distribution

Gender	*n*	BMI (kg/m^2)	Waist circumference (cm)	Total body fat %	Total body water %	Muscle mass (kg)	BMR (kcal)	Bone mass (kg)	Total cholesterol (mg/dL)	Mean HDL(mg/dL)	Mean non-HDL(mg/dL)	Log 25OHD (ng/mL)
Male	74	0.256[1]	0.256[1]	0.47[2]	-0.331[2]	-0.499[2]	-0.018	-0.206	-0.053	-0.139	-0.023	-0.479[2]
Female	93	0.377[2]	0.362[2]	0.322[2]	-0.271[2]	0.02	-0.332[b]	0.247[a]	-0.169	-0.176	-0.135	-0.102
Overall	167	0.239[2]	0.181[1]	0.445[2]	-0.364[2]	-0.426[2]	-0.047	-0.137	-0.72	-0.127	-0.045	-0.275[2]

[1]Correlation is significant at the 0.05 level (2-tailed);
[2]Correlation is significant at the 0.01 level (2-tailed). Univariate analysis was conducted and variables that had significant association with leptin in univariate analysis at $P < 0.2$ were considered in multivariable analysis. Coefficients (r) and P values are calculated using Pearson's correlation analysis. P-value less than 0.05 was considered as significant and < 0.001 as highly significant. BMI: Body mass index; BMR: Basal metabolic rate; 25OHD: 25-hydroxy vitamin D; HDL: High density lipoprotein.

shows that among various parameters (like BMR, female gender and bone mass) which were contributing towards leptin levels body fat percent with standardized beta weight of 0.488 was the most influential factor in leptin values followed by muscle mass (beta of -0.265) and 25OHD (beta of -0.253). Body mass index, waist circumference and body water percent were not good predictors for serum leptin. Statistics from multi-collinearity displayed tolerance < 10 indicating good associations with leptin. Moreover, muscle mass, bone mass, 25OHD and male gender showed a negative influence on leptin levels.

DISCUSSION

This study explored variables like anthropometric measurements, body composition, 25OHD and lipoproteins as predictors for serum leptin levels among representative population of healthy adults in Pakistan. Majority of the subjects were D deficient (89.2%). This is not surprising as previous published papers have shown high prevalence of VDD both in Pakistanis living abroad or residing in Pakistan[23,24]. Pakistan is among the sun-drenched countries and cutaneous production of vitamin D is possible throughout the year. However, despite this favorable climatic condition, research reports from our center showed widespread VDD[25-28]. Serum 25OHD showed non-significant and poor association with BMI in this study; contradicting to reports from other part of the world which showed inverse relationship of vitamin D with BMI[4]. The proposed hypothesis for could be attributed to Vitamin D lipophilic nature, that leads to 25OHD storage or sequestration in fat tissue. This volume-distribution effect could result in diminished vitamin D bioavailability and VDD in those with extra body weight. Reason for poor association of 25OHD with BMI could be that majority of our population was deficient in Vitamin D. Relationship could not be established as even non-obese subjects in this study were D deficient (88.7%). Similar trend was observed in previous study by our group, yet low vitamin D did not depict any change in BMD which may highlight the bone mineralization effects of raised leptin[29].

Obesity has been associated with both leptin and VDD[30,31]. Leptin regulates body fat mass and has a significant role in the control of body weight[32]. Leptin is directly associated with fat mass, circulating leptin molecules carry information to the brain (hypothalamus) regarding the energy stored in adipose tissue, diminishing appetite and affecting energy expenditure[33]. The receptors of leptin molecules are found in all places in the body indicating a general role[34]. Obesity is considered a leptin resistant state resulting in excessive growth of adipose tissue and high serum leptin levels. An indirect effect is of UVB radiation exposure and the latitude gradients on VDD and obesity. Hoseinzadeh *et al*[10] confirmed that the topographical factor varied with the variation in vitamin D levels in obese and the prevalence of VDD among African-American children and adolescents were 57% and 48.7% in Pennsylvania (latitude 40°N) and Wisconsin (latitude 43°N), respectively.

Going at par with VDD, obesity is also becoming a fast-growing health concern in Pakistan. Surplus body weight is a risk factor for many medical diseases, including cardiac disease, diabetes, arthritis and several cancers. According to recent studies, overweight and obesity have been shown to be related to low vitamin D status. For instance, according to a study in Oslo, Norway, the prevalence of VDD was highest in individuals with greater BMI regardless of their gender. Accumulating

Table 3 Multiple regression analysis of serum leptin determinants

Independent variables	Standardized β	*T* value	*P* value	95%CI for B	Collinearity statistics	
					Tolerance	VIF
BMI	0.017	1.057	0.292	-0.015-0.049	0.238	4.208
BMR	0.000	2.281	0.024	0.000-0.001	0.396	2.526
Muscle mass	-0.265	-2.995	0.003	-0.032-0.007	0.530	1.885
Body water (%)	0.308	1.875	0.063	-0.002-0.060	0.147	6.792
Body fat (%)	0.488	2.588	0.011	0.008-0.058	0.129	7.751
Bone mass	-0.191	-2.137	0.034	-0.032-0.007	0.523	1.912
Waist Circumference	-0.022	-0.201	0.841	-0.011-0.009	0.468	2.138
Log 25OHD	-0.253	-3.816	0.000	-0.720-0.232	0.944	1.060
Male gender	-0.186	-2.155	0.033	-0.419-0.018	0.522	1.916

Dependent variable: was log leptin. Univariate analysis was conducted and variables that had significant association with leptin in univariate analysis at $P < 0.2$ were entered in multivariable analysis shown above. Coefficients (r) and P values are calculated using Pearson's correlation analysis. BMI: Body mass index; BMR: Basal metabolic rate; 25OHD: 25-hydroxy vitamin D; HDL: High density lipoprotein.

epidemiological evidence suggests that hypovitaminosis D may be associated with obesity and related metabolic risks[35]. The levels of 25OHD are associated with BMI, declining with increasing BMI[36]. This is because adipocytes take up the Vitamin D from the blood, hence reducing the serum Vitamin D concentrations. This indicates that there is a link between Vitamin D levels and BMI which is a measure of relative weight based on an individual's mass and height. Hence, we hypothesized that lower Vitamin D levels would be noted with increasing BMI status among healthy individuals.

Similar to our study findings multiple studies have reported higher levels of leptin in females and this can be explained by differences in sex hormones[37,38]. Our study findings showed that male gender inversely contributed towards leptin levels with standardized beta weight of -0.253.

The present study has few limitations. Firstly, it was a cross sectional study hence causal relationship between leptin and other variables could not be determined. Secondly, the sample size was limited to predict any valid conclusion for a large set of population. Some gender-specific interlink was also noted, but absence of data of follicle stimulating hormone, luteinizing hormone, estradiol and testosterone levels could not allow the confirmation of this hypothesis. However, the study overall adds to the scientific knowledge of the burden of vitamin D in relation to healthy individuals.

In conclusion, this cross sectional study confirmed the relation between basal metabolic rate, muscle mass, body fat percent, bone mass, serum 25OHD and serum leptin levels. Additional studies are obligatory to define the role of hypothalamic control of body in bone formation. Elucidation of such mechanism may lead to a novel therapeutic approach to osteoporosis. Another question that remains unanswered is whether overweight/obese requiring more intense vitamin D supplementation to achieve optimal levels of 25OHD. It will also be interesting how weight loss or vitamin D treatment could affect leptin levels in this population.

ARTICLE HIGHLIGHTS

Research background

Obesity is considered a leptin resistant state leading to elevated leptin levels. Obesity in turn has also been linked to Vitamin D deficiency (VDD).

Research motivation

Going at par with VDD, obesity is also becoming a rapidly growing health problem in Pakistan. Obesity has been associated with both leptin and VDD. Few studies have attempted to investigate the effect of body composition and leptin with vitamin D in this part of the world.

Research objectives

We investigated the relation of serum leptin with body composition, lipids and vitamin D in adults.

Research methods

In a cross sectional study design bioelectrical impedance analysis was performed on 167 apparently healthy adults along with recording their demographics and clinical history. Blood was drawn for biochemical analysis of serum leptin, total vitamin D, total cholesterol and HDL cholesterol.

Research results

Majority of the study group was vitamin D deficient. Females had higher median leptin levels compared to their counterparts. Overall 17 (10.1%) study subjects had raised serum leptin levels with 88.2% of these subjects being Vitamin D deficient. Basic metabolic rate, muscle mass, bone mass, body fat percent, lipids and 25-hydroxyvitamin D (25OHD) and gender were associated with serum leptin levels. Bone and muscle mass and serum 25OHD bore an inverse relation with serum leptin.

Research conclusions

The cross-sectional nature of this study could not elucidate causal relationships. However, it outlines important interplay between circulating leptin, vitamin D and body composition. The results indicate that basal metabolic rate, muscle mass, body fat percent, bone mass and serum vitamin D have an impact on serum leptin levels. 25OHD did not vary between obese and non-obese. This probably could be because > 80% of the study group was D deficient.

Research perspectives

Future studies addressing the causal relationships between these essential molecules, leptin, vitamin D and lipids is needed to better understand their use as biomarkers of risk for obesity and diseases associated with obesity.

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