The effect of visfatin genotype on insulin pump therapy on quality of life in patients with type I diabetes

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ARTICLE INFO	ABSTRACT
	Diabetes is associated with an increase in other chronic diseases and an increase in mortality. The individual differences influence the treatment of this disease in pharmacokinetics and clinical responses. One of the important factors related to individual differences includes genetic factors in transmission, metabolism, and drug function. On the other hand, this disease has a significant impact on the patients' quality of life and their family. Therefore, this study aimed to investigate the role of single nucleotide polymorphism (rs2110385) of the visfatin gene on insulin required to maintain glucose homeostasis and to evaluate the effect of insulin pump therapy on the quality of life in type 1 diabetic patients. In this regard, this study was performed on 47 patients with type 1 diabetes. The short form of the Diabetes Quality of Life Questionnaire (DQOL) was used to record information. Laboratory tests also included FBS, HbA1C, G2h, serum levels of visfatin, insulin, and adiponectin. Insulin resistance (HOMA) and insulin sensitivity (QUICKI) indices were calculated. The polymorphism of the studied genotype was performed by the PCR-RFLP method. The results showed that the scores of both dimensions of quality of life, including patient care behaviors and satisfaction with the disease control after the intervention increased significantly (P <0.001). There was a significant and direct relationship between the patient's age and the duration of the disease with the score of increasing patients' quality of life. No significant differences were found between HbA1C, G2h, FBS levels, fasting insulin concentration, HOMA, and QUICKI indices. The insulin dose used to maintain glucose homeostasis at the same levels was significantly lower in the GG genotype than in other genotypes. In general, the present study results showed that insulin pump therapy and its dimensions could improve the life quality of patients with type 1 diabetes. Also, genetic evaluation of individuals helps to provide the correct and accurate dose of insulin with the help of the insulin pump for these patients to increase their quality of life as much as possible.

Introduction

Diabetes is widely recognized as a common disease in almost every country and age group and imposes enormous costs on communities (1). Diabetes causes complications in various organs of the body by involving microvascular and macrovascular. It can lead to vascular disorders, kidney failure, amputation, blindness, neurological diseases, dental diseases, pregnancy complications, heart disease, stroke, and even death (2).

Accordingly, diabetes can impair the life quality of the patient, their family, and their companions. There are several ways to control blood sugar (oral medications or insulin injections) (3). Still, the best treatment is a method that also improves the patient's quality of life in addition to controlling blood sugar

(4). Today, evaluating and improving people's life quality with chronic diseases is very important for health systems. The quality of life indicates a person's perception of functioning well at the physical, mental and social levels, especially in diabetic patients. Decreased quality of life reduces care, inadequate blood sugar control, and increases the risk of complications (5).

The onset of diabetes disrupts the normal rhythm of life. It requires daily monitoring of hypoglycemia through repeated daily insulin injections, blood glucose monitoring, and constant contacting with healthcare providers, strict exercise and diet plans, and disease control (6). Diabetes can threaten a person's independence and give a different feeling from others, which can cause stress. All these factors

affect a person's quality of life (7). Hypoglycemia is the most common side effect associated with type I diabetes, and in many cases, it can be controlled by regular insulin injections. Frequent injections and calculating the appropriate dose that needs to be completed at a specific time are the main concerns of insulin users (8).

Although some studies have shown that the insulin pump improves the quality of life, these patients need to achieve an accurate and appropriate dose of insulin (9). Recently, several studies have examined the importance of single nucleotide polymorphisms in response to insulin therapy (10, 11). Some of these studies have reported the association between genotypes and adipokines (also called adipocytokines), such as adiponectin, in response to insulin therapy (12).

Visfatin is an adipokine, formerly known as a pre-B cell colony enhancing factor (PBEF), which plays a vital role in glucose regulation (13). Previous studies have shown that people who are obese or suffering from diabetes have increased plasma visfatin concentrations (14, 15). On the other hand, it has been found that the serum concentration of visfatin is affected by glucose concentration. This effect can be changed by sensitivity to certain drugs (16). Recently, a study showed that by carefully controlling the blood glucose of diabetic patients, plasma visfatin levels and HbA1C levels are reduced together. Therefore, the decrease in insulin after pancreatic β-cell dysfunction can be compensated by changes in visfatin concentration (15).

Recent studies on the promoter region of the visfatin gene have identified single nucleotide polymorphisms, some of which are related to diabetes and glucose homeostasis. The visfatin gene's coding region or regulatory region polymorphisms are associated with plasma glucose levels, 2-hour blood glucose, and insulin levels (17).

According to the effect of visfatin gene polymorphism on glucose homeostasis (18), this study was designed to evaluate the impact of SNP(rs2110385) located in the visfatin gene promoter region on insulin resistance, insulin sensitivity, and the appropriate dose of an insulin pump for each patient based on their genotype to improve their life quality.

Materials and methods
Survey population and anthropometric assessments

The study included 47 patients with type I diabetes referred to the medical training center between May 2019 and April 2020. An endocrinologist diagnosed with type I diabetes and at least six months after the onset of the disease is considered the entry criterion. The exclusion criteria included previous use of the insulin pump, dissatisfaction with further research, inability to learn to use the insulin pump, severe hypoglycemia, pregnancy, or mental retardation. By selecting 90% confidence level, 90% power, and effect size equal to 0.25 (the maximum effect size in the Kohn equation) and using 11G * power 3.1.9.2 software, the required sample size was calculated to be 42 people that 47 people were checked for possible falls. Therefore, 47 patients were sampled through the census.

Conscious consent was obtained from each patient to participate in the study, and they were assured that their identities were confidential. Regarding children, obtaining consent and explaining the objectives of the study to parents was done. After reviewing the inclusion and exclusion criteria, the questionnaires were completed by interviewing the questionnaire for patients. The questionnaire consisted of questions about personal factors and the short form of the Diabetes Quality of Life Questionnaire (DQOL). The individual factors questionnaire included age, gender, weight, height, body mass index or BMI, duration of illness, level of education, residency, marital status, occupation, and underlying diseases. The quality of life questionnaire for people with diabetes (DQOL) consists of 90 questions. It was first reduced to 15 questions in 2004 by Burroughs et al. (19) its internal stability was 0.77, and its retest reliability was 0.73. The validity of the 15-item quality of life questionnaire for type 1 and 2 diabetic patients in the Greek version was assessed, and its high fact was reported with Cronbach's alpha of 0.95 (20). The Malaysian version confirmed with Cronbach's alpha of 0.703 and was evaluated in type 2 diabetic patients (21).

In the present study, comprehensive and sufficient explanations were given about the research objectives and the confidentiality of information for participation

in the study. The questionnaires were completed before using the insulin pump, and the questionnaire was completed six months after using the insulin pump. To begin treatment with an insulin pump, patients and their parents were first given intensive training on how to use an insulin pump and monitor glucose levels. Data before and after the study were recorded and analyzed in the questionnaires.

Laboratory evaluations

Venous blood samples were taken from patients who were fasting for 10-12 hours and stored at 80°C immediately after centrifugation and serum separation for laboratory tests. Glycosylated hemoglobin (HbA1C) was measured by ion-exchange HPLC using DS5 England, and the values were expressed as a percentage. Plasma glucose levels ('FPG) were determined by GOD/PAP method. Oral glucose tolerance test (OGTT2) was performed according to the standard of the World Health Organization (22). Accordingly, patients were given 75 g of glucose dissolved in 250 ml of water after 12 hours of fasting, and sampling was performed after 120 minutes to determine the serum glucose concentration using GOD/PAP method (redox laboratory method). ELISA determined serum visfatin level with a sensitivity of 30pg/ml and with a coefficient of variation of within-group and between-group evaluation of 4.3% and 7.5%, respectively (Human visfatin ELISA kit, AdipoGen Pharmaceuticals, Belmont, Seoul, Korea).

Plasma insulin concentration was assessed by ELISA method with a sensitivity of 1.76µlU/ml and with coefficients of intragroup and intergroup variation of 2.19% and 4.4%, respectively (Human insulin ELISA kit, DRG Pharmaceuticals, GmbH, Germany).

HOMA and QUICKI calculations

Insulin resistance was calculated by homeostasis model assessment (HOMA) according to the following formula (23):
Insulin resistance = fasting plasma glucose × level Plasma insulin fasting level / 22.5
Insulin Sensitivity Index or QUICKI was calculated according to the following formula (24):
ISQUICKI = 1 / [log (fasting insulin) + log (fasting glucose)]

DNA extraction and Genotyping

The HigherPurity™ Blood DNA Extraction Kit (LifeScience, USA) was used to extract DNA from peripheral blood. The extracted DNA was stored at 4°C for PCR and RFLP reactions. Genomic DNA of all individuals was evaluated to determine the G or T nucleotide at position -4689G/T of the visfatin gene by the RFLP-PCR method. Primers for sequence amplification include:
Forward 5'TCCCCCAAGCTGTTATGGTA3'
Reverse 5'AAGGTATGGTTGACCCAGCTA3'
Restriction endonucleases HindIII was used for RFLP detection part.

Statistical analysis

Frequency and percentage indices were used to describe the data for qualitative variables, mean and standard deviation were used for quantitative variables with normal distribution, and median and quadratic amplitude was used for abnormal quantitative variables. The Kolmogorov-Smirnov test investigated normal distribution. Fisher's exact test or chi-square test was used for qualitative variables. Independent t-test or parametric analysis of variance was used for normal quantitative variables, and Kruskal-Wallis non-parametric analysis of variance was used for quantitative abnormal variables. The paired t-test was used for the normal quantitative variables to examine the difference between before and after variables. Wilcoxon symptomatic rank non-parametric test was used for slightly abnormal variables. The correlation between quantitative variables and quality of life was performed based on the Spearman correlation coefficient test. We considered a significance level of five percent in all tests, and statistical analysis was performed by SPSS software version 15.

Results and discussion

In this study, the age range of type 1 diabetic patients was between 3 and 61 years, with a mean age of 17.64 ± 11.39 years. The majority were female (57.4%, number = 27). Most patients (34%) were children, 31/9% were single, and 17% were married. In this study, patients' mean weight was 62.30 ± 25.83 kg, the mean height was 161.02 ± 13.80 cm, and the mean BMI was 23.44 ± 5.85. The duration of the

disease was reported to be 100.94 ± 91.51 months. In this study, 72.3% of people stated that they do not have another disease (Tables 1 and 2).

Table1. Quantitative study variables and their correlation with changes in quality of life during the study

Variable	The Least	The Most	Mean ± SD	Correlation with Changes in Life Quality	
				Spearman Coefficient	Significance (P)
Age (year)	3	61	17.64 ± 11.39	0.365	0.015
Duration of Disease (month)	7	432	100.9 ± 91.5	0.306	0.039
BMI (kg/m^2)	14.61	36.68	23.42 ± 4.35	0.059	0.716

According to the relationship between individual variables and changes in the life quality of diabetic patients during the study, there was no significant relationship between gender (P = 0.71), marital status (P = 0.104), and other diseases (P = 0.98) with changes in patients' quality of life score (Table 2). However, there was a significant and direct relationship between the mean age and duration of the disease with the change in patients' quality of life after using the pump. So that older people (r = 0.365, P = 0.015) and longer disease duration (r = 0.306, P = 0.039) had a higher quality of life score after using the pump. Also, no significant relationship was observed based on the correlation test between the BMI variable and change in patients' quality of life (r = 0.059, P = 0.716) (Table 1).

Table 2. Qualitative variables of the study and the average results of changes in life quality in terms of qualitative variables

Variables	Level	Number (Percent)	Middle (mid-quarter range)	P-value
Gender	Male	20 (42.6%)	13.5 (4.26 - 5)	0.706
	Female	27 (57.4%)	17 (5 - 20)	
Marital Status	Single	15 (31.9%)	17 (13 -22)	0.104
	Married	8 (17%)	23 (11 - 31)	
	Child	16 (34%)	11 (3 -20)	
	Missing	8 (17%)	12.5 (2.75 – 18.75)	
Other Diseases	Having	13 (27.7%)	14 (7.24 – 15)	0.98
	Not Having	34 (72.3%)	15 (4.22 – 15)	

According to the findings of Table 3, the mean of life quality score for type I diabetic patients and its dimensions (patient care behaviors and satisfaction with disease control) increased significantly after the intervention compared to before (p <0.001). Also, the rate of change in the quality of life of the studied patients was reported to be significant (p <0.001).

Table 3. Results of quality of life dimension scores before and after the study

Variable		Before Intervention	After Intervention	The amount of change	P-value
Patient care behavior		19.59 ± 4.79	26.68 ± 6.22	7.08 ± 7.40	<0.001
Satisfaction with disease control		18.63 ± 4.44	25.04 ± 6.50	6.40 ± 6.36	<0.001
Quality of life score		38.23 ± 7.95	51.72 ± 12.15	13.48 ± 12.61	<0.001
Quality of life level	15-29	4	4	-	<0.001
	30-44	35	10	-	
	45<	8	36	-	

The biochemical characteristics of the study participants are shown in Table 4. Of these patients, 53.19% had poor glycemic control (7% HbA1C), and the rest (46.81%) had reasonable glycemic control. The prevalence of polymorphism genotypes studied in this study for GT, GG and TT was 31.2%, 50.5%, and 18.3%, respectively. Also, 60.63% of patients had the G allele, and 39.37% had the T allele. Blood glucose control status was not associated with visfatin gene alleles, with poor glycemic control in 54.38% of cases with G allele and 51.53% of T allele cases.

Table 4. Biochemical characteristics of study participants

Biochemical Characteristics	Mean ± Standard Deviation
FBS (mg/dl)	159 ± 68
OGTT (mg/dl)	199 ± 83
Hb A1C (%)	7.4 ± 1.7
HOMA	5.3 ± 2.8
QUICKI	0.50 ± 0.06
Fasting insulin level (µlU/ml)	14.2 ± 6.8
Serum concentration of visfatin (ng/ml)	14.69 ± 14.02
Mean energy intake in patients (kcal)	1998 ± 1566
Insulin dose (unit)	4 ± 3

The results of laboratory evaluations and insulin dose among different genotypes are shown in Table 5. The results presented in Table 5 show a significant difference between the doses of insulin required to control blood sugar among different genotypes in patients with diabetes. The amount of insulin that patients need to control blood sugar in the GG genotype is lower than in other genotypes.

Table 5. Patient characteristics based on genotype

Variable	Genotype		
	TT	GT	GG
FBS (mg/dl)	162 ± 61	160 ± 81	156 ± 62
Two hours of sugar (mg/dl)	185 ± 29	206 ± 90	195 ± 96
Hb A1C	6 ± 0.4	7.4 ± 1.8	7.7 ± 2.1
HOMA	4.02 ± 1.46	5.98 ± 3.16	5.09 ± 2.58
QUICKI	0.52 ± 0.05	0.49 ± 0.06	0.51 ± 0.07
Fasting insulin level (µlU/ml)	11.41 ± 5.53	15.74 ± 7.50	13.52 ± 5.88
Serum concentration of visfatin (ng/ml)	15.85 ± 18.45	12.88 ± 14.13	14.79 ± 13.75
Insulin dose (unit)	6 ± 2	5 ± 1	4 ± 2

One of the objectives of this study is to evaluate the effect of insulin pump therapy on the quality of life of patients with type 1 diabetes. This study showed that the mean of life quality scores and dimensions of type 1 diabetes patients after the study were significantly improved compared to before the study. In addition, after using the pump, the number of people with high quality of life was significantly higher than before the study.

In the present study, the life quality of individuals before using the pump was 38.23 ± 7.95, and after the intervention was 51.72 ± 12.15. In this regard, Muller-Godeffroy et al. (25) conducted a study entitled "Investigation of quality of life and family burden issues during insulin pump therapy in children with type 1 diabetes mellitus". They found that after a continuous shift of insulin pump subjects with continuous subcutaneous injection, the quality of life of children with diabetes in all age groups increased significantly. It also reduced overall parental stress and concerns about hypoglycemia. For parents of younger children (6-7 years old), the problems they had with nutrition were reduced. In 2008, Nuboer et al. (26) conducted a randomized, prospective comparative study of the effect of insulin pump versus injectable therapy on quality of life and the impact of the disease in children with type-1 diabetes. In this study, an in-group comparison of patients showed that using an insulin pump improved metabolic control, the frequency of severe hypoglycemia, quality of life, and the effect of disease scores compared to regular treatment with four daily insulin injections. Another study found that pump therapy was an effective means of insulin therapy in young patients with type 1 diabetes; which indicates improved glycemic control by reducing the frequency of blood sugar. Quality-of-life measures indicate that psychosocial symptoms may also improve following this treatment (27). Other studies performed on type 1 diabetic patients using the DQOL questionnaire had similar results. All of them showed an increase in quality of life score after using the pump and had positive effects on its dimensions, such as self-care and patients' satisfaction with controlling the treatment of the disease (28-30).

According to the results of the mentioned studies, it seems that the psychological and social improvement of patients and the relative stability of their biochemical factors play an essential role in improving their quality of life (8). These are the same factors that have already been mentioned in the definition of quality of life (31). This definition showed that quality of life includes the dimensions of mental, physical, and social health, performance in life, and roles in life and public welfare. The first area of existence is material existence, which includes physical fitness, personal hygiene, nutrition, exercise, cleanliness, clothing, and general physical appearance (32). The second area is psychological existence, including mental health and adjustment, cognition (such as perception, attention, and memory), emotions, self-esteem, self-concept, and self-control (33). The third area is spiritual existence, including personal values, personal behavioral criteria, and spiritual beliefs. "Belonging" similarly includes three areas: physical belonging, social belonging, and community belonging, and all these factors play a role in the theoretical model of life quality (34).

However, contrary to the results of the above studies and the present study, a survey by Rosner *et al.* (32), which was performed on diabetic patients using an insulin pump and daily injection, showed that the quality of life in people who use an insulin pump with continuous subcutaneous injection and long-term glycemic control is not significantly different from daily insulin injections (32). In assessing the quality of life of type 1 diabetic patient (9 to 17 years old), Rendell *et al.* (35) found that the dimensions of quality of life in patients who used insulin pumps were similar to those who received repeated daily injections. A study was conducted to determine the changes in glycemia and its effect on the quality of life in adults with type 1 diabetes. The results show that insulin pump therapy with continuous subcutaneous injection is associated with slight glycemic changes compared to the daily injection method. However, this study did not show an association between glycemic changes and quality of life in adults with type 1 diabetes. Regardless of whether they were in the daily injection group, insulin pump, or continuous subcutaneous injection group, there was no significant difference in the quality of life between the two treatment groups (36).

Regarding genotypic assessments, fasting insulin levels are low in patients with TT genotype. As a result, patients with the TT genotype need higher insulin doses to control their blood sugar. At the same time, this difference is not significant in GG genotype. Since there was no significant difference between glycemic control indices (G2h. FBS and Hb A1C) between genotype types, the difference in genotype is the main factor in determining the required dose of the drug among patients.

Several studies have investigated the role of inflammatory factors such as adipocytokines and genotype in glucose homeostasis and patients' response to antidiabetic drugs (37-40). Zhang *et al.* (41) evaluated the effect of +45 adiponectin mononucleotide polymorphism in response to tax rosiglitazone treatment in patients with type 2 diabetes. A total of 103 people with diabetes who did not receive any blood glucose control drugs were included in the study and were given a dose of 4 or 8 mg of rosiglitazone tax per day to control their blood sugar for 24 weeks. The results of their research did not show a significant difference in response to treatment among genotypes.

In general, the present study results showed that insulin pump therapy and its dimensions, including patient care behaviors and patient satisfaction could improve the life quality of patients with type 1 diabetes. Also, genetic evaluation of individuals helps to provide the correct and accurate dose of insulin with the help of the insulin pump for these patients to increase their quality of life as much as possible.

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