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Is there a role of inulin in the management of type 2 diabetes mellitus ?!

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Abstract

Background: Type 2 Diabetes mellitus is a serious disease; its prevalence is rising to pandemic levels worldwide. Hypertriglyceridemia is a feature of the disease. It is a main culprit behind the cascade of the biochemical disorders of type 2 diabetes mellitus. Inulin fructose is an edible oligosaccharide. It exerts a prebiotic effect on colonic microbiota, enhancing the bifido bacteria strains; their products stimulate the gut endocrine L-cells to secrete glucagon like peptide-1 which improves insulin resistance.

Methods: Twenty eight obese type 2 diabetic female patients, each of them was given four grams inulin fructose daily as an add on therapy to their conventional antidiabetic treatment for three weeks. Their fasting serum triglycerides, insulin resistance, fasting insulin level and fasting glucose level were estimated before and after three weeks of inulin intake.

Results: There was a significant decrease in the serum level of the aforementioned four parameters.

Conclusion: Inulin can be given as an add on treatment to conventional antidiabetic therapy. It effectively reduced serum triglycerides and insulin resistance which is the core problem in the management of type 2 diabetes mellitus.

Keywords: Inulin, Type 2 diabetes, Triglycerides. Insulin resistance, Insulin.

Introduction

Type 2 diabetes mellitus is the most common type of diabetes encountered in daily clinical practice. It accounts for 90-95% of diabetic patients[(1,2)]. It afflicts an appreciable sector of mankind allover the globe. The prevalence is about 7-10% in the different countries; and an equal number masquerades undiagnosed[(3,4)]. Undoubtedly we are in the midst of an epidemic of this disease[(5)]; and it is anticipated that by the year 2025 these figures will double which means a pandemic spread worldwide[(2)].

Type 2 diabetes mellitus is usually met with in obese persons and individuals with the metabolic syndrome. These obese patients have increased fat content in their adipose tissue and in their omenta. Lipolysis of this fat results in the flux of increased amounts of free fatty acids (FFA) and triglycerides in the different

cells of the body organs[6,7]. The increased storage of FFA, triglycerides and their metabolites (diacylglycerides & ceramides) in the different tissue cells produces a state of lipotoxicity.

Lipotoxicity of the liver cells is associated with reduced ability of insulin to stimulate metabolic pathways in the liver itself and in other tissues: skeletal muscles and adipose tissue[8]. Insulin resistance is considered a major starting pathophysiological step in the course of type 2 diabetes mellitus; which leads to the subsequent pathogenic events that characterise type 2 diabetes and aggravates its course[9].

Inulin is a safe oligosaccharide of the fructose type, which has been used in several experimental and few human studies in the field of diabetology[10-12]. It exerts prebiotic effects mainly by changing the composition and activity of gut microbiota[10]. It also exerts beneficial effect on glucose intolerance, the metabolic syndrome and serum triglycerides; As it enhances the gut bifidobacteria to produce certain peptides which stimulate tne endocrine gut L cells to secrete glucagon like peptide-1 (GLP-1); This latter improves hepatic insulin resistance and energy metabolism[11-15].

The aim of the present work is to evaluate, how far inulin fructose acts in the control of the different pathological disorders which affect energy metabolism.

Subjects and Methods

Subjects:

Twenty eight type 2 diabetic females aged 40 to 65 years; were selected from the clinics of the governorate hospitals. These constitute the subjects of the present study. Their selection was according to the following criteria.

Inclusion criteria: females, type 2 diabetics, overweight or obese, hypertensive or not.

Exclusion criteria: Patients were free of any acute or chronic condition or disease which might affect the metabolic status of the patient such as:

- Acute or chronic bacterial infection like skin infection or ulcers or carbuncles or infected foot or gangrene.
- Cancer lesion in any organ.
- Any endocrine gland disorder such as thyroid or suprarenal.
- Under hormonal therapy or contraceptive pills.
- Organ decompensation: Heart, lung, liver or kidney.

Ethical committee approval: This work was approved by the ethics committee of the National Research Centre (NRC)-Egypt ethical certificate approval number 15 011.

Concent: Each patient was asked to sign a written concent for her agreement to be enrolled in the study.

Methods

Each patient ingested four grams of inulin-type prebiotic daily. Two grams in the morning and two grams in the evening for three weeks.

Inulin intake by the patients, was an add on therapy to their conventional daily treatment of their diabetic state.

Inulin specifications: Inulin A.R ($C_6H_{10}O_5$) N ALPHA-CHEMIKA Mumbai. 400002 (INDIA) An ISO: 9001: 2000 Certified company.

Each patient was subjected for the following investigations before the start of inulin ingestion and after three weeks later. i.e. at the end of inulin intake period.

1. Fasting serum triglycerides estimation: quantitative determination of serum triglycerides was done spectrophotometrically according to Fossati[16] using the kit from Centronic Germany.

2. Insulin resistance (IR) was assessed using homeostasis model assessment (HOMA) from fasting serum glucose and fasting serum insulin level, after Mathiews et al. [17]
3. The equation: insulin resistance (HOMA-IR) = fasting glucose (mg/dl) x fasting insulin (μ I.U./ml)/ 405.
4. Fasting serum insulin estimation: This was quantitatively estimated using an enzyme immunoassay method according to National Committee for Clinical Laboratory Standards.[18] Manufacturer of the kit used: immunospect corporation 7018 Owensmouth Ave. Suit 103 Canoga Park, CA, 91303.
5. Fasting serum glucose determination: This was estimated by an enzymatic colorimetric method. The principal is enzymatic oxidation of glucose by glucose oxidase enzyme, according to Tietz[19].
   Kit used from Egyptian Company for biotechnology (S.A.E.) Obour City Industrial Area. block 20008 piece 19A Cairo. Egypt.

   EC – REP – MDSS GmbH – Schiffgraben 41 – 30175 Hannover, Germany.

Statistical Methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp. Chicago, USA, 2013.

Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as mean±SD (standard deviation) for quantitative parametric data. Inferential analysis were done for quantitative variables using paired t-test in cases of two dependent groups with parametric data. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

Results

Table (1) shows body mass index (BMI) of the type 2 diabetic female patients enrolled in the study.

Table (2) shows the mean ± SD of each of the four determined parameters which are involved in glucose metabolism before and after inulin intake.

Table (3) shows a significant positive correlation between fasting serum insulin level and insulin resistance (IR) before and after inulin intake. r=0.897 & P 0.001 before inulin intake; while r=0.932 & P 0.001 after inulin intake.

The following figures are reported before and after inulin intake respectively:

- Mean fasting serum triglycerides in mg/dl was 245.6 ± 105.7 and 201.4 ± 95.5.
- Mean insulin resistance (IR) was 11.1 ± 8.2 and 7.2 ± 5.0.
- Mean fasting serum insulin in μ I.U/ml was 15.3 ± 8.9 and 12.3 ± 7.6.
- Mean fasting serum glucose in mg/dl was 298.3 ± 70.0 and 242.6 ± 59.8.
- Figure 1 shows a significant positive correlation between fasting serum insulin level and insulin resistance which is the core problem in the pathogenesis of type 2 diabetes mellitus.
- Figures 2, 3, 4 and 5 show a significant decrease of the fasting serum levels of the different parameters involved in glucose metabolism after inulin intake; the parameters are fasting serum triglycerides, insulin resistance, fasting serum insulin level and fasting serum glucose level.

Table (1): Body mass index (BMI) of the type 2 diabetic female patients enrolled in the study.

Number of patients	Mean±SD	Range
28	**34.9 ±5.1**	**25.4 - 47.9**

Table (2): Laboratory findings among the studied cases before and after inulin intake.

	Before		After		^Change		#P
	Mean±SD	Range	Mean±SD	Range	Median (IQR)	Range	
Triglycerides (mg/dl)	245.6±105.7	91.0–434.0	201.4±95.5	80.0–392.0	-41.5 (-58.5–-28.5)	-115.0–-2.0	<0.001*
Insulin Resistance (IR)	11.1±8.2	2.5–32.1	7.2±5.0	2.1–18.7	-3.5 (-5.4–-1.6)	-13.4–2.7	<0.001*
Fasting Insulin (µI.U/ml)	15.3±8.9	4.0–29.4	12.3±7.6	2.9–26.1	-2.8 (-5.2–-1.4)	-9.9–5.0	<0.001*
Fasting Glucose (mg/dl)	298.3±70.0	210.0–450.0	242.6±59.8	129.0–303.0	-38.5 (-101.0–-8.3)	-175.0–82.0	<0.001*

N=28, ^Negative values indicate reduction, #P-value of paired t-test, *Significant

Table (3): Correlation between fasting serum insulin level and insulin resistance (IR) before and after inulin intake

Before inulin intake	After inulin intake
r 0.897	r 0.932
P 0.001	P 0.001

The table shows a significant positive correlation between fasting serum insulin and insulin resistance (IR) before and after inulin intake.

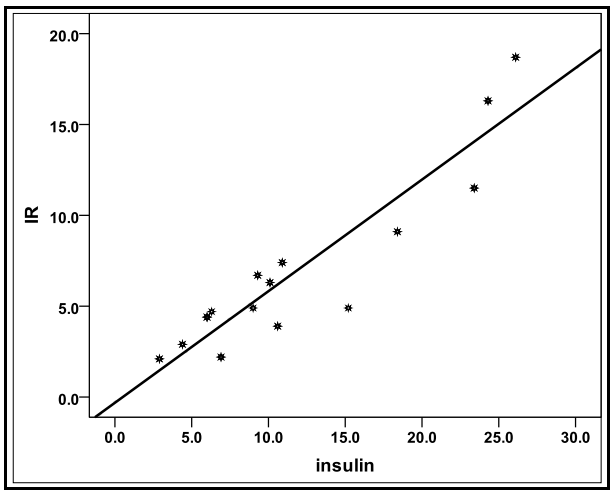

Figure (1): Figure shows a significant positive correlation between fasting serum insulin level and insulin resistance (IR).

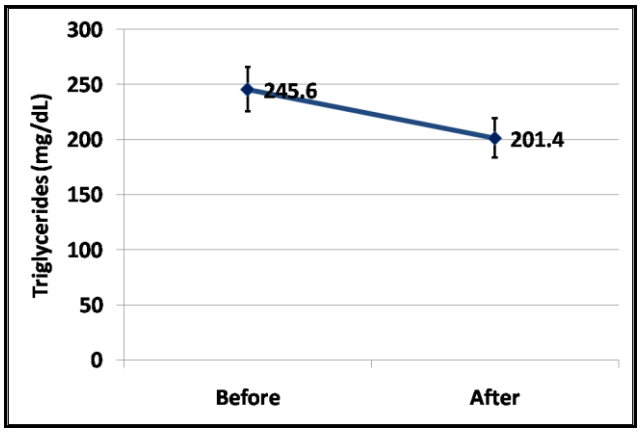

Figure (2): Serum triglycerides (mg/dl) before and after inulin intake. Triglycerides decreased significantly after inulin intake.

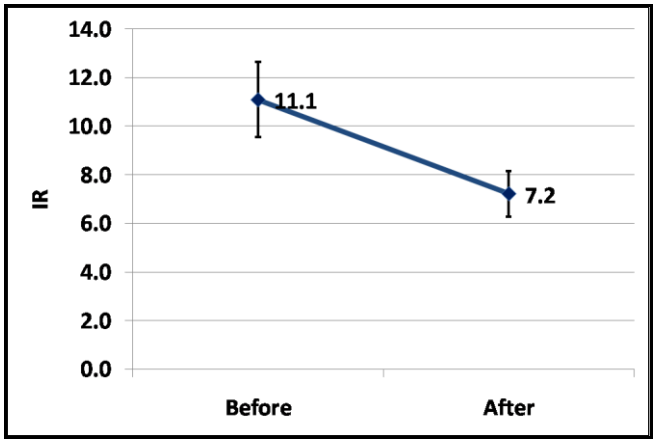

Figure (3): Insulin Resistance (IR) before and after inulin. (IR) significantly decreased after inulin intake.

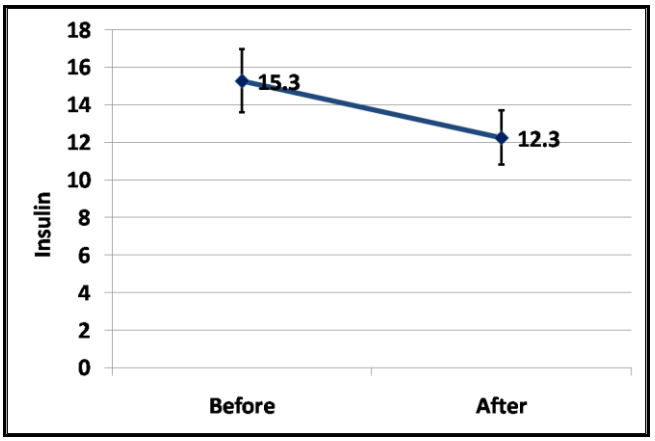

Figure (4):Serum insulin level µI.U/ml before and after inulin. The level significantly decreased after inulin intake.

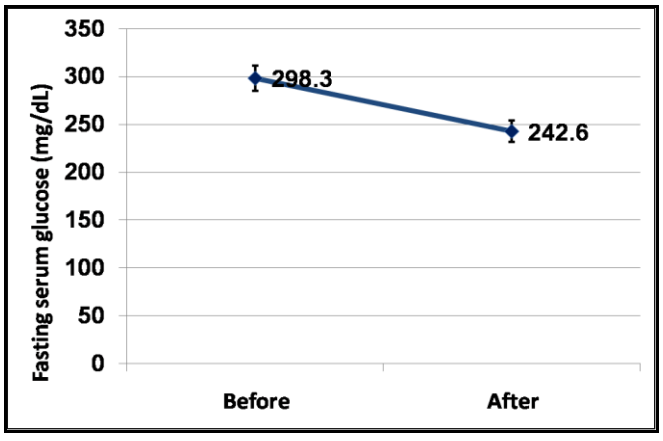

Figure (5):Fasting serum glucose (mg/dl) before and after inulin.Glucose level significantly decreased after inulin intake.

Discussion

In recent years, it has been realized that, both hepatic steatosis and hepatic insulin resistance go hand in hand and are intimately related.

Peripheral insulin resistance, on the other hand, is also the consequence of intrahepatic fat accumulation. Insulin resistance starts primarily in the liver as the first site; followed by insulin resistance in the peripheral tissues, namely the skeletal muscles and the adipose tissue[20, 21].

The view that, the liver is the primary site for insulin resistance is not a new one. A hepatic humoral factor which stimulates muscle uptake of glucose was proposed to be lacking in fatty liver[22, 23]. Recently, experimental work on insulin receptors (in liver, muscles and adipose tissue) Knock out mice emphasized that insulin resistance starts in the liver as the primary site followed by insulin resistance in peripheral tissues[24]. More recently, this fact has been supported by the finding of over expression of glycerol-sn-3-phosphate acyl transferase 1 in rats, which causes hepatic steatosis, insulin resistance and triglycerides accumulation in the gastrocnemius muscle of the rat[25].

In humans, similar conclusions were also reported. The relation between peripheral insulin resistance and intrahepatic fat content was much stronger than with intramyocellular fat content, visceral fat content or subcutaneous fat content[26-28].

In our present study on type 2 diabetic female patients, inulin intake significantly reduced serum triglycerides level.

In another study on type 2 diabetic patients (data not shown here – in press), we also determined the liver fat content of the patients after inulin intake by the use of liver fat index (LFI) after Bedogni et al[29]. That study showed significant decrease in the LFI after inulin intake. Other workers, using experimental animals reported improvement in hepatic steatosis after inulin ingestion[30].

In fact, fatty liver is strongly associated with fasting plasma insulin concentration; At the same time circulating plasma insulin is recognized as a discrete surrogate of insulin resistance[31].

In the present work in the same patients, we also determined other important parameters related to glucose metabolism namely, insulin resistance using (HOMA equation), fasting serum insulin level and fasting serum glucose level. These three parameters significantly decreased after inulin intake by the patients; From these results, the following consequences of events can be deduced. Lowering serum triglycerides, improved both fatty liver and insulin sensitivity; the latter was shown by the decreased insulin resistance (HOMA equation). The improved insulin sensitivity raised its ability to stimulate the metabolic pathways of glucose in the different tissues of the body. This resulted in a lower fasting serum glucose level. Blood glucose, being the most important stimulus for insulin secretion; its decreased blood level, resulted in a lower fasting serum insulin level.

However, in the literature, some workers used high doses of inulin prebiotic ranging from ten to twenty grams per day and reported insignificant results[32,33]. Other workers also used large doses of inulin prebiotic daily and reported significant results[34]. These discordant results can be explained in view of the following facts: First, a minimal dose of inulin-type prebiotic appears to be needed to enhance the bifidobacteria strains[35].In the present study, we used four grams of inulin daily. Second, inulin type prebiotic can either be extracted from certain plants, for example from chicory roots; or synthesized from other molecules such as sucrose[35]. During the process of manufacturing, free monosaccharides (fructose and glucose) are yielded in varying amounts. The more the amount of free monosaccharides, the more the bias which might affect the final results during their study; this might be a factor. Besides, the longer the chain of inulin, the stronger the results (High Performance Inulin)[36]. Third, prebiotics are a group of more or less similar compounds collectively termed inulin type prebiotics. These include inulin fructans, fructose oligosaccharides (FOS) and oligofructose. All three differ in the length of their molecular chain which might impact the final results between their study[36]. Current evidences suggest that inulin fructans but not FOS or oligofructose might influence serum lipids in hyperlipidemic individuals[36,37]. Forth, the genetic constitution of the host harbouring the bacteria is important[38]. Again, mice lacking toll-like receptor five (TLR-5) - an important component of the innate immune system, are prone to develop insulin resistance[39].

In conclusion, inulin seems to be a valuable compound as it might prove to be a useful effective treatment in type 2 diabetes mellitus, It tackles several important points in the chain of disorders of carbohydrate metabolism; most importantly it targets the chief core problem of the disease namely insulin resistance; In this way it reduces the endogenous hyperinsulinemia which, itself can perpetuate insulin resistance in peripheral tissues: skeletal muscles and adipose tissue[40,41].

Besides, it can be used as an add on treatment, as it might help in reducing the hypoglycemic attacks which oftenly accompany conventional treatment with insulin or with insulin secretagogue drugs. It thus protects the patient against in advertant or aggressive treatment.

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