EFFECT OF DIET AND OTHER FACTORS ON SERUM ADIPONECTIN CONCENTRATIONS IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Background. Adiponectin is a protein specific to visceral adipose tissue where its concentrations are reduced in type 2 diabetes and obesity. Many factors also determine serum levels of adiponectin such as gender, BMI, as well as diet.

Objective. To compare the effects of consuming certain key foodstuff products on serum adiponectin concentrations between diabetic patients and suitable controls.

Material and methods. A survey and laboratory testing was performed on 72 patients of whom (n = 21) were diabetics, whilst the control group, (n = 51) non-diabetics. Eating habits were assessed and serum adiponectin was measured in all cases.

Results. Diabetic patients had significantly lower adiponectin levels compared to the control group; respectively (23.5±21.1 µg/ml vs. 36.5±21.1 µg/ml; p=0.02). Furthermore, women had higher concentration than men; respectively (41.3 µg/ml± 20.1 µg/ml vs. 22.0 µg/ml± 14.8 µg/ml; p=0.000). A high consumption of foodstuffs such as vegetables, vegetable oils, coffee and tea positively correlated with adiponectin concentration in serum, whilst a negative correlation was seen with consumptions of mixed bread, fried and baked dishes, alcohol, nuts and seeds.

Conclusions. Serum adiponectin levels are related to factors such as gender, (higher in women), BMI, (higher in persons with normal body weight) and whether diabetic, (lower in people with diabetes). Multiple correlations were observed between the consumption of foodstuff product groups and serum adiponectin concentration. It is thereby suggested, that adiponectin could have a significant role to play in the treatment and prevention of diabetes and obesity.

Key words: *adiponectin, diabetes, diet, eating habits*

STRESZCZENIE

Wprowadzenie. Adiponektyna jest białkiem swoistym dla tkanki tłuszczowej wisceralnej. Zmniejszone jej stężenie obserwuje się w cukrzycy typu 2 oraz otyłości. Istnieje wiele czynników determinujących poziom adiponektyny w surowicy krwi tj. płeć, BMI, ale również dieta. Celem pracy była ocena wpływu spożywanych grup produktów na poziom adiponektyny w surowicy krwi osób z cukrzycą oraz grupy kontrolnej.

Materiał i metody. Badaniem ankietowym oraz analizą laboratoryjną objęto 72 pacjentów. Grupę badaną (n=21 osób) stanowiły osoby chore na cukrzycę, natomiast grupę kontrolną (n=51 osób) stanowiły osoby bez cukrzycy. Ocenie poddano sposób żywienia oraz zawartość adiponektyny w surowicy krwi pacjentów.

Wyniki. Adiponektyna osiągała niższe wartości u osób z cukrzycą w porównaniu do grupy kontrolnej (23,5±21,1 µg/ml vs. 36,5±21,1 µg/ml; p=0,02). Kobiety charakteryzowały się wyższym jej stężeniem w stosunku do mężczyzn (41,3 µg/ml± 20,1 µg/ml vs. 22,0 µg/ml± 14,8 µg/ml; p=0,000). Wysoka częstość spożycia produktów spożywczych takich jak: warzywa, oleje roślinne, kawa i herbata dodatnio korelowała ze stężeniem adiponektyny w surowicy krwi. Natomiast spożywanie pieczywa mieszanego, potraw smażonych i pieczonych, alkoholu, orzechów i pestek było ujemnie skorelowane ze stężeniem adiponektyny w surowicy krwi.

Wnioski. Wykazano, że poziom adiponektyny w surowicy krwi zależy od czynników takich jak: płeć (wyższy u kobiet), BMI (wyższy u osób z prawidłową masą ciała) oraz obecności cukrzycy (niższy u osób z cukrzycą). Zaobserwowano wiele korelacji dotyczących częstości spożycia produktów, a stężeniem adiponektyny w surowicy krwi, co też może odgrywać znaczącą rolę w leczeniu oraz profilaktyce cukrzycy oraz otyłości.

Słowa kluczowe: *adiponektyna, cukrzyca, dieta, zwyczaje żywieniowe*

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INTRODUCTION

Diabetes is a 'disease of civilisation' whose increase is slowly becoming to be considered an epidemic, thereby constituting a serious problem in public health. Undoubtedly addressing this issue is also a priority of the medical establishment, where disseminating information/knowledge on how to prevent or treat this disease is vital, as well as introducing new and more effective therapeutic methods.

Many studies have demonstrated the beneficial and protective effects of adiponectin against type 2 diabetes and obesity occurring. Adiponectin is a 30KD peptide, specific to adipose tissue and secreted into the circulation, but is also synthesised by cardiomyocytes. The N-terminus consists of a fibrous conformation whereas the C-terminus is globular; the structure resembling TNF-α. The gene encoding adiponectin, (APM 1) is regarded as one of those that are candidates in type 2 diabetes thanks to mapping of the human genome [17]. This gene is located on chromosome 3q27, where a susceptibility locus is present for Type 2 diabetes and metabolic syndrome. In the bloodstream, adiponectin exists in 3 oligomeric structures (fractions), differing in molecular weight, consisting of low molecular weight, middle molecular weight and high molecular weight forms; respectively termed LMW, MMW and HMW. There exist 2 types of adiponectin receptor, (AdipoR1 and AdipoR2), that are present in all tissue, however they differ in their organ distribution and gene location [18]. Decreased blood concentrations of adiponectin are seen in obesity, type 2 diabetes (related to insulin resistance), atherosclerosis, hypertension, coronary artery disease and stroke; in fact low concentrations of adiponectin may be responsible for developing type 2 diabetes [18, 19]. Furthermore, higher adiponectin concentrations are found in women than men. It is intriguing that higher levels of adiponectin are seen in people with an appropriate body mass, but not in those who are obese even though it is being produced in adipose tissue. A possible explanation for this paradox, is that increased secretion of other adipokines may inhibit adiponectin production as well as the permeability and lipid loading of adipocytes that is observed in obesity, where adiponectin production is suppressed. Confirmation of this however requires further study [18].

The anti-diabetic action of adiponectin depends on increasing insulin sensitivity in the liver, through deceasing the influx of free fatty acids, increasing hepatic fatty acid oxidation, and in skeletal muscle, lowering liver gluconeogenesis and stimulating fatty acid oxidation in muscle tissue [18, 23]. In muscle cells, adiponectin activates the expression of proteins responsible for transport and β-oxidation of fatty acids (Acetyl CoA oxidase, PPAR-γ), which intensifies thermogenesis [2]. Apart from decreasing liver gluconeogenesis, the anti-diabetic action of adiponectin can therefore be explained by increasing glycolysis in skeletal muscle. However, when liver gluconeogenesis inhibition is lessened, due to adiponectin deficiency, then this could lead to hyperglycaemia [18, 23].

When assessing changes in serum adiponectin levels, a vital aspect are genetic influences. Mutations in the AMPI region, caused by substituting thiamine with guanine, results in decreased adiponectin concentrations in the bloodstream which in turn results in increased risk of insulin resistance, type 2 diabetes and atherosclerosis [2, 17, 26]. There are also reports that vegetarian and Mediterranean diets positively affect adiponectin serum levels [8, 14].

The study aim was to assess the effect of how often a group of chosen foodstuffs were consumed (ie. consumption), on serum adiponectin concentrations in those patients with diabetes compared to non-diabetic controls.

MATERIAL AND METHODS

The study comprised of 72 patient subjects attending the Department of Endocrinology, Diabetology and Internal Medicine at the University Clinical Hospital in Białystok who freely gave their consent to be surveyed and have their blood analysed. Previously, the study had received approval by the Bioethics Commission at the aforementioned hospital (No. R-I-002/35A/2011).

The study group consisted of 21 diabetic patients, 6 women (28.6%) and 15 men (71.4%) whilst the control non-diabetics were 34 women (66.7%) and 17 men (33.3%). Those with diabetes were aged 51 ±10 yrs on average, and those from the control group 34 ±15 yrs. Nutritional status was assessed by the BMI for which ≤25.0 kg/m2 was considered appropriate whilst 25-29.9 kg/m2 overweight and ≥30.0 kg/m2 as obese. The mean BMI of the diabetic group was 29.8 ±6.6 kg/m2 whilst for controls this was 26.7 ±6.4 kg/m2. Those in the former group consisted of 19% with appropriate BMI, 47.6% were overweight and 33.3% obese. The corresponding breakdown for the non-diabetics were 49% with appropriate BMI, 21.6% were overweight and 29.4% obese.

Blood was obtained from fasting patients and levels of glycated haemoglobin and glucose measured enabling the 2 groups to be thus defined. Serum adiponectin was also measured by I125 radioimmunoassay, and related to patients' nutritional status and nutrition; counts being recorded on a Wallac 1275 minigamma counter (LKB Wallac, Turku, Finland).

The questionnaire assessed consumption levels for specific groups of foodstuffs/products divided into weeks or months. Data were entered into a Microsoft Excel Spreadsheet and then analysed by Statistica 9.0 software. The non-parametric *Man-Whitney* U test was used to evaluate serum adiponectin results for the significance of differences between groups. The rank *Spearman* correlation (R) was used to test for relationships between consumption of foodstuff products and serum adiponectin concentration; p<0.05 was adopted as the critical value for significance.

RESULTS

The non-diabetic controls had significantly higher mean adiponectin concentrations in the serum of 36.5 ±21.1 µg/ml (range 9.2-106.1 µg/ml) than diabetic patients 23.5 ±21.1 µg/ml (range 3.5-48.7 µg/ml); p=0.02. Within the diabetic group, there was also a significant difference between adiponectin concentrations for women and men; respectively 37.6 ±12.5 µg/ml and 17.8 ±11.7 µg/ml, p=0.01. A somewhat similar result was seen for the non-diabetics; for women 42.0 ±21.2 µg/ml and 25.7±16.4 µg/ml for men (p=0.005).

The relationships between nutritional status and serum adiponectin concentrations showed the following; no significant differences in adiponectin concentrations between the 3 BMI categories for the diabetics (Table 1), whilst a significant difference in adiponectin was seen between those with an appropriate BMI and the obese group (p=0.024) for the non-diabetic controls (Table 1). Furthermore, non-diabetic obese patients had significantly lower adiponectin compared with those having an appropriate BMI within same group; respectively 26.1 ±15.0 µg/ml (range 10.2-56.2 µg/ml) vs 44.7 ±22.4 µg/ml (range 9.2-106.1 µg/ml), p=0.024.

Consumption of various bread products in diabetics was significantly and negatively correlated with adiponectin concentrations (p=0.049, R=-0.435). A significantly positive correlation (p=0.047, R=0.439) was however seen in the same group between seed and nuts consumption vs adiponectin concentration. This was in contrast to the non-diabetics, where a negative correla-

tion was observed between the seeds and nut consumption and adiponectin levels (p=0.017, R=-0.332). The non-diabetic controls, who were overweight, showed a negative correlation (p=0.012, R=0.722), between consuming roasted foods and adiponectin concentrations as well as those foods that were fried (p=0.032, R=-0.646 respectively). Within this same group, the consumption of vegetables with adiponectin was positively correlated (p=0.007, R=0.757). The non-diabetics, who were obese, showed a negative correlation between vodka consumption and adiponectin (p=0.03, R=-0.56). In those non-diabetics but with appropriate BMI (n=25), there were both positive correlations between consumption of coffee or tea with adiponectin; respectively (p=0.024, R=0.45) and (p=0.046, R=0.403).

DISCUSSION

Adiponectin is only one such substance amongst the adipokines that are secreted by adipose tissue, and its decrease in serum is highly correlated to obesity, type 2 diabetes, insulin resistance and triglycerides concentration; women are known to have higher concentrations to men [3, 25], which is confirmed by the presented study (overall results being 41.3 ±20.1 µg/ml for women and 22.0 ±14.8 µg/ml in men, p<0.05). In addition, the current study also confirms that diabetics have lowered adiponectin serum concentrations compared to non-diabetics; 23.5 ±21.1 µg/ml and 36.5 ±21.1 µg/ml respectively. This pattern has been seen in other studies, eg. *Żurawska-Klis* et al. [30] showed respectively levels of 7.26 ±4.42 µg/ml vs 13.76 ±21.1 (p=0.001). A study by *Knobler* et al. [12] measured serum adiponectin in patients with glucose intolerance and coronary artery disease which demonstrated that in those patients who developed type 2 diabetes then adiponectin concentrations were much lower than those without this disease; respectively 4.1 µg/ml (3.9-4.4 µg/ml) vs 4.6 µg/ml (4.3-4.9 µg/ml). It seems therefore, that adiponectin assumes a protective role in the development of diabetes, including those who have a higher propensity for acquiring the disease [12]. The present study confirms this, together with others, thus suggest-

Table 1.   Plasma adiponectin concentration in patients with normal weight, overweight and obesity in both groups (diabetics and non-diabetics)

Examined group	Obesity		Overweight		Normal weight	
	Diabetics	Non-diabetics	Diabetics	Non-diabetics	Diabetics	Non-diabetics
n	7	15	10	11	4	25
Average concentration (µg/ml)	30.5	26.1*	14.6	32.2	33.3	44.7*
±SD (µg/ml)	15.7	15.0	8.0	18.6	16.6	22.4
Minimum value (µg/ml)	9.4	10.2	3.5	13.0	11.1	9.2
Maximum value (µg/ml)	48.7	56.2	28.1	68.8	48.7	106.1

* difference statistically significant; p<0.05

ing that adiponectin is an independent factor affording protection against type 2 diabetes. It should be noted that serum adiponectin levels were much higher in the study than the others cited; a possible explanation being in the very wide range of concentrations observed.

As mentioned previously, serum adiponectin is lower in men compared to women as witnessed by the current study and also those quoted. A further study in healthy Koreans, (*Park* et al.), showed a similar trend where there was a 30% reduction in adiponectin levels in men compared to women, ie. 6.2 ±3.3µg/ml vs 9.1±4.7µg/ml [19], thus confirming the aforementioned trend [6]. Indeed, other studies show that androgens decrease serum adiponectin concentrations [1, 16, 32].

The current study investigated whether adiponectin levels were related to BMI (nutritional status), where there were no relationships observed in the diabetic group. The non-diabetics, however, demonstrated higher adiponectin in those with correct body weight compared with obese subjects (p=0.024). Although this trend was not observed in the study by *Żurawska-Klis* et al., a negative correlation was recorded between adiponectin levels and the waist to hip ratio (WHR), of R=-0.31, p<0.05, [30]. In this instance, it was concluded that adiponectin negatively correlated with the amount of visceral adipose tissue, ie. with stomach obesity, even though there was no correlation seen with BMI. Another study by *Bai Jie* et al. in fact show a weak negative correlation between BMI and serum adiponectin (R=-0.33, p=0.02) [1], as did a study by *Kim* et al. (R=-0.452, p<0.001) [11]. It therefore seems likely that nutrition may be related to serum adiponectin concentration.

Consumption of specific foodstuff groups and serum adiponectin was also investigated by the presented study; a significant negative correlation being seen with the consumption of mixed bread and adiponectin in diabetics (R=-0.453, p=0.05), which may be explained by such bread mixes not having a low glycaemic index like wholemeal products. A study by *Qi* et al. demonstrated that consuming foodstuffs, with a high glycaemic index and glycaemic load, causes low serum adiponectin levels, however fibre-rich diets of low glycaemic index results in an increase in diabetic men [22]. Another study by this group also showed that wholegrain fibre consumption, together with vegetable fibre, were significantly related to increased adiponectin; respectively p=0.02 and p=0.036, [21].

The presented study revealed that vegetable consumption and serum adiponectin were positively correlated (R=0.757, p=0.007) in non-diabetics who were overweight. This may reflect that vegetarian and Mediterranean diets (also rich in vegetables) has a beneficial effect on serum adiponectin levels [8, 14]. A study by *Kahleova* et al. assessed the effect a vegetarian test diet (vs a typical diet over 24 weeks) had on improving insulin sensitivity in type 2 diabetes; after 24 weeks, adiponectin levels significantly rose in the test group vs controls (p=0.02). Nevertheless, it should be noted that the test group had much lower levels of visceral adipose tissue (p=0.007), which may have affected the observed increases of adiponectin [8].

There was a positive correlation seen between adiponectin and fruit consumption (R=0.08, P<0.01), wholegrain products (R=0.14, p<0.01) and nuts (R=0.06, p=0.07) in a study by *Mantzoros* et al. conducted on women suffering from type 2 diabetes. It was further demonstrated that women who consumed >15g alcohol/24hrs, had higher serum adiponectin than those consuming less [14]. The reasons for the wide variations seen in these studies so far described requires further investigations. It may be that the properties of dietary fibre vary according to source, where some may contain other substances/factors that may interfere.

The current study shows that some fats affect serum adiponectin levels; a negative correlation being seen in all subjects, taken together, between pork consumption (with a high fat content), and adiponectin (R=-0.265, p=0.024). A positive correlation was however observed for diabetics between vegetable oil consumption and adiponectin (R=0.439, p=0.047), as was the same relationship in overweight diabetics (R=0.784, p=0.007). In contrast, for non-diabetics, a negative correlation was found between seed and nut consumption and adiponectin (R=-0.332, p=0.017). A study by *Kalgaonkar* et al. investigated the effects of consuming polyunsaturated fat (PUFA n-3/n-6), from nuts and monounsaturates (MUFA), from almonds in women with polycystic ovary syndrome on various endocrine and metabolic parameters (eg phospholipids, LDL cholesterol, Apoliprotein B, as well as adiponectin). Dietary nuts and almonds were found to lower LDL cholesterol and Apolipoprotein B (p=0.05 and p=0.03 respectively), whereas both increased adiponectin (p=0.0241 and p=0.0262 respectively) [9]. Another study [29] looked at whether PUFA affects levels of PPAR-γ (peroxisome proliferator activated receptor-γ). This receptor is responsible for increasing insulin sensitivity and the appropriate maturation of adipocytes. Mice were fed a diet rich in saturated and polyunsaturated fat (given as fish oil) that increased serum adiponectin levels, suggesting that this may mediate the effect of PUFA. A study by *Martins* et al. evaluated the effect of Conjugated Linoleic Acid (CLA) and saturated fats on adiponectin and fatty acids in obese and diabetic rats fed on a diet containing palm oil and sheep fat, which was subsequently enriched with CLA. This dietary enrichment increased adiponectin serum concentrations and sheep fat increased levels of leptins and insulin resistance compared to palm oil [15]. The findings of the presented study, together with those of studies quoted, thus show that different types of fat

variously affect serum adiponectin levels. The negative correlation found between seed and nut consumption and adiponectin is however, in contrast to those studies cited. A reason for this, is that the presented study treats these products as one group whereas those quoted treat them separately. Nevertheless, the other wide variations seen, require further investigation on the effect fat consumption has on adiponectin levels.

Various report show that little-moderate alcohol consumption can reduce the likelihood of type 2 diabetes and the current study found a negative correlation between vodka consumption and serum adiponectin ($R=-0.56$, $p=0.03$) in obese non-diabetics. Differences in serum adiponectin concentrations between the genders and alcohol consumption were also examined by *Imhof* et al., in which women and men respectively consumed 20g and 30g daily. It was found that women drinking red wine had increased adiponectin levels ($p<0.05$) and likewise in men, that drank sprits or beer ($p<0.05$ for both); non-alcoholic drinks showed no effect [7]. In similar fashion a study by *Beulens* et al. demonstrated that after 4 weeks, those men who daily consumed 30g alcohol had 12.5% higher adiponectin levels ($p<0.001$) than controls (where water had replaced alcohol consumption); the HMW fraction having risen by 57% ($p=0.07$), the MMW by 12.5% and the LMW remaining unchanged [4]. A further study by *Thamer* et al. found that serum adiponectin was higher in those men drinking alcohol twice or more weekly ($p=0.05$), than those abstaining; likewise in women, those abstaining had lower adiponectin compared to those who drank occasionally (2-3 times per week) or more that 5 times a week ($p=0.03$) [27]. In summary, the results from the current study were different to the literature; a possible reason being that in the latter, alcohol was consumed often but in small quantities whilst in the former, alcohol was drunk infrequently but in higher amounts. This however requires further confirmation by new studies.

Tea and coffee consumption were found to be positively correlated with serum adiponectin levels ($R=0.45$, $p=0.024$ and $R=0.403$, $p=0.046$ respectively). A study to test the risk of coffee consumption and type 2 diabetes (*Kempf* et al.) demonstrated that drinking 8 or more cups of coffee per day significantly increases adiponectin in the serum ($p<0.05$) [10]. A study conducted on Afro-American women, *Boggs* et al. confirmed that consuming moderate amounts of alcohol and coffee reduces the risk of type 2 diabetes; ie. drinking 4 coffee cups or more, compared to those abstaining ($p=0.03$) - no effects with tea or de-caffeinated coffee having been detected [5]. A study by *Kotani* et al., performed in Japan, however found no effect of coffee consumption on adiponectin serum levels. The authors suggest that ethnic considerations may have played a part, but that this requires further probing for confirmation [13].

Further studies, are therefore vital to determine the role that adiponectin plays in human physiology as this could form the basis for future treatments of disorders such as diabetes, obesity or coronary artery disease; given the alarming increases seen in their incidences, particularly for diabetes. A carefully considered strategy of prevention or treatment would greatly benefit those patients suffering from these kinds of illnesses and could in the future reduce their numbers.

CONCLUSIONS

1. Significantly higher serum levels of adiponectin were found in non-diabetics than diabetics. Nutritional status also affects adiponectin concentration (ie. is greater in those with appropriate BMI); there are also gender differences where women have higher levels.
2. Additionally, the role of dietary foodstuffs consumed in diabetes or obesity occurring may be through regulation by serum adiponectin. These relationships however, require further study for more precise definition and to exclude other factors that may also play their parts.

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