Original Article

Serum Adiponectin Variation and its Relationships with Certain Markers of Cardiovascular and Metabolic Risk in Type 2 Diabetes

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Abstract

Introduction: adiponectin seems to participate in the pathophysiology of comorbidities associated with obesity such as type 2 diabetes. Thus, we propose to determine the correlation of serum adiponectin to clinico-biological parameters in type 2 diabetes.

Methodology: this is a case-control study with a bio-anthropometric and a biochemical examination in all participants. The arterial stiffness and the endothelial dysfunction were evaluated. Serum adiponectin and nitric oxide levels were measured by the ELISA sandwich test.

Results: serum adiponectin was significantly lower in type 2 diabetic subjects ($p<0.0001$). In the control group, serum adiponectin was correlated positively with HDL cholesterol ($r=0.279$ $p=0.005$) and negatively with body mass index ($r=-0.339$ $p=0.001$), waist-hip ratio ($r=-0.290$ $p=0.004$), visceral fat level ($r=-0.246$ $p=0.014$), glycated hemoglobin ($r=-0.215$ $p=0.004$), insulin resistance index ($r=-0.391$ $p<0.0001$), apolipoprotein B–apolipoprotein A ratio ($r=-0.226$ $p=0.024$) and total cholesterol/HDL cholesterol ($r=-0.199$ $p=0.047$). In the diabetic group, serum adiponectin was correlated positively with HDL cholesterol ($r=0.331$ $p=0.001$) and fingers-toes pulse wave velocity ($r=0.228$ $p=0.024$), and negatively with heart rate ($r=-0.224$ $p=0.027$), reactive hyperhemic index ($r=-0.364$ $p=0.126$), total cholesterol ($r=-0.212$ $p=0.034$), and triglycerides/HDL cholesterol ($r=-0.223$ $p=0.026$).

Conclusion : serum adiponectin decreases with obesity. It would protect against insulin resistance and cardiovascular dysfunction during type 2 diabetes.

Keywords: adiponectin, obesity, type 2 diabetes, vascular dysfunction

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Introduction

Diabetes mellitus is one of the most common chronic noncommunicable diseases in the world [1]. Type 2 diabetes contributes to 95% of all diabetes mellitus [2]. It is enamelled with a heavy morbi-mortality attributable to its cardiovascular complications.

Cardiovascular complications during diabetes would have as its base atherosclerosis. Impaired vascular function, namely endothelial dysfunction and arterial stiffness, initiates and maintains the development and the progression of atherosclerosis.

Obesity remains a primary risk factor for the development of type 2 diabetes [3, 4]. Most patients with type 2 diabetes are or have been obese, the increase in the prevalence of type 2 diabetes is closely linked and attached to that of obesity so that their collective increase is called "diabesity". Obesity is defined as an excessive increase in the body's adipose tissue in such a proportion that it can influence the state of health [5]. The pathophysiological links between obesity and type 2 diabetes involve lipid metabolism disorders and insulin resistance.

Several molecules secreted by different parts of adipose tissue regulate various important parameters within the body through cascades of metabolic reactions [6]. They are commonly called adipokine [7], and they are among the main regulatory molecules controlling the balance of lipid and carbohydrate metabolism. Adiponectin is an adipokine [8], and is suggested to play a possible role in mediating cardiometabolic diseases, inflammation, and their sequelae.

Major changes have taken place in the diagnostic and therapeutic approach to chronic non-communicable cardiometabolic diseases, thanks to the advent of high-throughput technologies and advances in molecular biology. This has led to the development of the search for new biomarkers of cardio-metabolic diseases.

It is in this perspective that we proposed to carry out this study whose general objective was to evaluate the profile of serum adiponectin levels and its determining factors during type 2 diabetes.

Methodology

Subjects and Protocol

In total, 100 control and 100 type 2 diabetic were included in this study. We included women aged at least 18 years.For patients, the diabetes known and followed for at least 2 years.We didn't include breastfeeding or pregnant women, diabetic subjects with severe complications or comorbidity. All participants provided signed informed consent.

All procedures were conducted in accordance with the standard of the Helsinki declaration.

Clinical procedures

All subjects were interviewed on demographic characteristics, personal history and lifestyle habits.

A measurement of anthropobiometric and cardiovascular parameters was carried outfrom each subject.

The vascular function investigations were based on the evaluation of the endothelial function by measuring the reactive hyperhemic index (RHI) by EndoPAT2000® and of the arterial stiffness by determining the finger-toe pulse wave velocity (ft-PWV) by pOpmeter®.

Biological assays

Blood samples were taken the same daybefore the interview sessions after a 12-hour night-time fastingfor the determination of fasting blood glucose, glycated hemoglobin, circulating lipids the kidney and liver function.

The method of enzyme-linked immunosorbent assay was using for the quantitative determination of total nitric oxide serum (Assay Catalog Number KGE001)and of serum adiponectin concentrations (Assay Catalog Number DRP300), all 96 wellsof R&D systems, Bio-techne, Minnesota, USA.

Statistical analyzes

The data exploitation was carried out by SPSS Statistics software. The quantitative variables were described using mean ± standard deviation and

median with quartiles. The qualitative variables using absolute values and percentages. The pair comparisons between the different groups were evaluatedby Student T, ANOVA, Wilcoxon and Friedman tests. The Spearman correlation test was used to evaluate the relationships between serum adiponectin and the other parameters. The results were considered significant when p≤5%.

Results

Comparison of clinical and cardiovascular characteristics

We find that type 2 diabetic were more obese according to the waist-hip ratioand their heart rate is higher, see table 1.

Table 1: Comparison of clinical characteristics

Variables	Control	Diabetic	p value
Age (years)	50.01 ± 7.97	51.50 ± 7.53	0.159
Waist hip ratio	0.85 ± 0.08	0.89 ± 0.07	<0.0001
Body mass index (kg/m^2)	29.12 ± 6.22	28.86 ± 5.41	0.756
Total body fat mass (%)	41.67 ± 6.39	40.31 ± 6.38	0.153
Visceral fat level	9.17 ± 3.06	9.06 ± 2.95	0.801
Heart rate (bpm)	76.28 ± 10.93	84.06 ± 11.88	<0.0001
Systolic blood pressure (mm Hg)	134.05 ± 23.95	136.39 ± 27.33	0.524
Diastolic blood pressure (mm Hg)	88.86 ± 14.99	87.14 ± 13.74	0.403
Nitric oxide (µmol/l)	742.83 ± 257.01	768.89 ± 235.30	0.456
Ft-PWV (m/s)	8.20 ± 3.27	9.30 ± 4.66	0.064
RHI	2.07 ± 0.69	1.87 ± 0.64	0.520

Compare to control,we noted a significantly extent insulin resistance (p=0.001), lower HDL cholesterol (p=0.001) and a higher LDL cholesterol(p=0.0003) in diabetic. The risk of atherosclerosis according to the Castelli indices (Total cholesterol/HDL cholesterol, LDL cholesterol/HDL cholesterol, Triglycerides/HDL cholesterol and Apolipoprotein B/Apolipoprotein A) was significantly higher in diabetic (respectively, p<0.0001, p<0.0001, p<0.0001, p=0.049), see table 2.

Table 2: Comparison of biochemical parameters

Variables	Control	Diabetic	p value
Fasting blood sugar (g/l)	0.86 ± 0.16	1.51 ± 0.80	<0.0001
Glycated hemoglobin (%)	5.29 ± 0.65	8.06 ± 2.33	<0.0001
IR-HOMA	2.23 ± 0.22	6.15 ± 1.16	0.001
C peptid (ng/ml)	1.22 ± 0.91	1.16 ± 0.65	0.607
Total cholesterol (g/l)	2.11 ± 0.42	2.19 ± 0.48	0.209
Triglycerides (g/l)	0.79 ± 0.32	0.90 ± 0.45	0.059
HDL cholesterol (g/l)	0.60 ± 0.14	0.53 ± 0.15	0.001
LDL cholesterol (g/l)	1.38 ± 0.38	1.60 ± 0.48	0.0003
Total cholesterol / HDL cholesterol	3.60 ± 0.75	4.34 ± 1.31	<0.0001
LDL cholesterol / HDL cholesterol	2.40 ± 0.82	3.24 ± 1.35	<0.0001
Triglycerides / HDL cholesterol	1.39 ± 0.68	1.88 ± 1.25	<0.0001
Apolipoprotein B / Apolipoprotein A	0.66 ± 0.22	0.79 ± 0.61	**0.049**

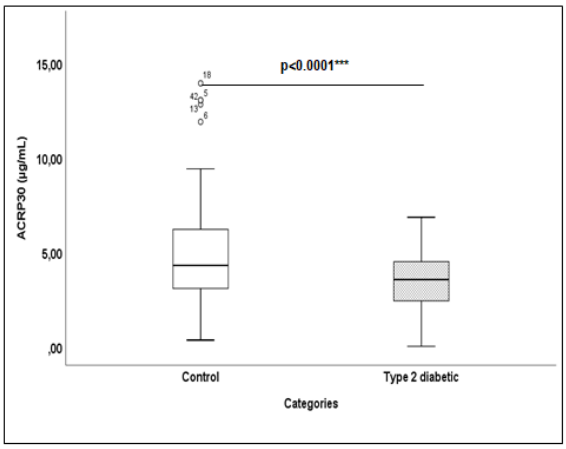

Figure 1 : comparison of serum adiponectin levels between the two study groups *p≤0.05, **p≤0.01, ***p≤0.0001

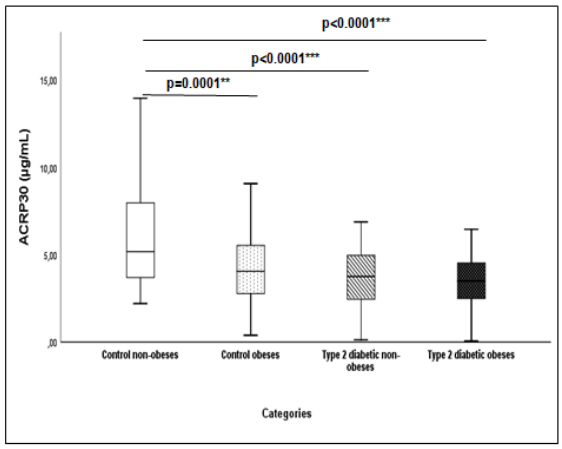

Figure 2 : comparison of serum adiponectin levels according to the body mass index status in the two study groups. *p≤0.05, **p≤0.01, ***p≤0.0001

We noted a lower serum adiponectin level in type 2 diabetic with a statistically significant difference compared to control (p<0.0001), see figure 1.

The serum adiponectin levels are lower in obese, non-obese diabetic and obese diabetic with a significant difference compared to control (respectively, p<0.0001, p<0.0001, p<0.0001), see figure 2.

Measures of association between serum adiponectin levels and the other parameters in each study group

Correlations between serum adiponectin levels and the different clinical parameters

We observed a negative correlation between serum adiponectin and anthropo-biometric parameters, and significantly in the control group. A negative correlation was noted between serum adiponectin and heart rate in type 2 diabetic, see table 3.

Table 3: Correlation between serum adiponectin and anthropo-biometric parameters

ACRP30 (µg/ml)	Control		Diabetic	
	Coefficient r	p value	Coefficient r	p value
Age of participants (years)	0.126	0.213	0.141	0.160
Body mass index (kg/m²)	- 0.339	0.001	- 0.062	0.538
Waist hip ratio	- 0.290	0.004	- 0.027	0.792
Visceral fat level	- 0.246	0.016	- 0.012	0.905
Total body fat (%)	- 0.173	0.088	- 0.011	0.915

Correlations between serum adiponectin and the vascular parameters

Table 4 shows that in diabetic, the serum adiponectin was correlated positively with the fingers-toes pulse wave velocity, and negatively with the heart rate and the nitic oxide.

Table 4: Correlation between serum adiponectin and cardiovascular parameters

ACRP30 (µg/ml)	Control		Diabetic	
	Coefficient r	*p* value	Coefficient r	*p* value
Systolic blood pressure (mm Hg)	- 0.011	0.913	- 0.021	0.840
Diastolic blood pressure (mm Hg)	- 0.045	0.659	- 0.149	0.144
Heart rate (bpm)	-0.058	0.585	- 0.224	0.027
Nitric oxide (µmol/l)	-0.429	0.095	- 0.223	0.026
Ft-PWV (m/s)	0.019	0.866	0.228	0.024
RHI	- 0.168	0.337	- 0.364	0.126

Correlations between serum adiponectin and biochemical parameters

The table 5 shows a negative correlation between serum adiponectin and the HOMA-IR, total cholesterol and triglyceride/HDL cholesterol ratio, and a positive correlation between serum adiponectin and HDL cholesterol.

Table 5: Correlation between serum adiponectin and carbohydrate-lipid parameters

ACRP30 (µg/ml)	Control		Diabetic	
	Coefficient r	*p* value	Coefficient r	*p* value
Fasting blood glucose (g/l)	- 0.069	0.492	- 0.092	0.363
Glycated hemoglobin (%)	- 0.215	0.032	- 0.136	0.179
IR-HOMA	- **0**.391	<0.0001	- 0.181	0.073
C peptid (ng/ml)	- 0.168	0.094	- 0.027	0.787
LDL cholesterol (g/l)	- 0.117	0.247	- 0.120	0.235
Triglycerides (g/l)	- 0.098	0.331	- 0.098	0.332
Total cholesterol (g/l)	- 0.071	0.483	- 0.212	0.034
HDL cholesterol (g/l)	0.279	0.005	0.331	0.001
Total cholesterol/HDL cholesterol	- 0.199	0.047	- 0.148	0.140
LDL cholesterol/HDL cholesterol	- 0.091	0.366	- 0.105	0.299
Triglycerides/HDL cholesterol	- 0.195	0.052	- 0.223	0.026
Apolipoprotein B/Apolipoprotein A	- 0.226	0.024	- 0.051	0.612

Discussion

We conducted a cross-sectional study from a cohort of control and type 2 diabetic patients.The study objective was to evaluate the profile of serum adiponectin levels and its determinants during type 2 diabetes mellitus.

We noted a lower serum adiponectin level in diabetic compared to control. This means that adiponectemia would decrease during type 2 diabetes. Our results are in the same direction as the data in the literature. Numerous studies have focused on variations in its serum levels and the onset of type 2 diabetes [9]. They almost all noted an association between hypoadiponectinemia and the development and progression of type 2 diabetes [10].

The serum adiponectin is inversely proportional to obesity stigma (body mass index, waist-hip ratio, visceral fat level). We noted a lower serum adiponectin levels in the obese, non-obese diabetic and obese diabetic subjects with a significant difference compared to control. Our results corroborate the literature data. In a sample of obese women compared to non-obese women, serum adiponectin is negatively correlated with waist-hip ratio, body mass index, and global body fat [11, 12]. In other studies, 21% weight loss increased serum adiponectin levels by 46% [13], whether in diabetic and non-diabetic subjects (40% à 60%) [14]. Adiponectin is the only adipose tissue protein whose levels decrease with obesity [15].

The serum adiponectin is inversely proportional to the insulin resistance stigma (fasting blood glucose, C peptide, HbA_1c, and HOMA-IR).This finding supports the results of other previous studies. An experimental study found an association between adiponectin and the development of insulin resistance [16]. Adiponectin level would already be reduced in the pre-diabetic phase and would evolve in parallel with the decrease in insulin sensitivity [17, 18].For some authors, the adiponectin level would be more related to the insulin resistance degree than to the adiposity degree [11]. According to the same authors, the adiponectin concentration is positively correlated with insulin sensitivity and decreases significantly with the decline in glucose tolerance [11].

The serum adiponectin is negatively correlated with total cholesterol, LDL cholesterol and triglycerides and it is positively correlated with HDL cholesterol. A study has shown that the administration of adiponectin is associated with a reduction in

circulating fatty acid levels and an increase in their oxidation, thus inducing a decrease in triglycerides content in skeletal muscles [17]. In the same study, the author showed that the reduction in the serum fatty acids levels would rather result from the acceleration of their tissue absorption. Furthermore, several studies have observed a significant and positive association between serum adiponectin levels and HDL cholesterol concentrations [19]. Adiponectin is therefore involved in lipid and lipoprotein metabolism [9].

Serum adiponectin was negatively correlated with cardiovascular constants and Castelli atherogenic risk indices. In additional, serum adiponectin would be elevated if markers of subclinical atherosclerosis were present (increased ft-PWV and decreased nitric oxide and RHI). Our results suggest a protective role of adiponectin against the cardiovascular diseases risk including atherosclerosis. These results seem to agree with those of other studies. Adiponectin positively modulates endothelial functions [20]. Authors have observed that adiponectin plays a role in maintaining the integrity of the vessel wall [18]. It has also been reported that low serum adiponectin levels in diabetic constitute a predictor of macro-angiopathy [14] and that high levels of adiponectin are actually cardio protective [21]. Low serum adiponectin level in type 2 diabetes would indeed be an indicator of the development of macro-angiopathies and would increase the risk of atherosclerosis [10].

Through its ability to improve insulin sensitivity and correct the lipid profile, the high concentration of adiponectin would act as a protector of the metabolic and cardiovascular system, independently of traditional risk factors for cardiovascular diseases [22]. Adiponectin is an adipocytokine with pleiotropic signal effects [23]. Thus, several mechanisms could explain its protective role in diabetogenesis and atherogenesis.

In the liver, adiponectin decreases glycogenesis by suppressing the fatty acid flux and inhibiting the glycogenesis enzymes expression. It increases the expression of proteins involved in fatty acid metabolism[17]. Ouchi et al also observed that adiponectin would inhibit monocyte adhesion [24]. Adiponectin also modulates endothelial functions and has an inhibitory effect on the proliferation of smooth muscle cells, and on the transformation of macrophages into foam cells [20].

The strengths of this study lie in the quality of the manipulations carried out by the same practitioner and at the same time.

The limitation of this study lies in the fact that we have a study population taken only from the female population and the non-inclusion of children.

Conclusion

Adiponectin interacts with carbohydrate and lipid metabolisms, and it contributes to the functional mechanisms of the vascular wall. It plays a role in protecting against insulin resistance, type 2 diabetes and its cardiovascular complications. It would be involved in the pathophysiological metabolic transition between obesity and type 2 diabetes.

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