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ARE THERE ANY SUBSTANTIAL DIFFERENCES IN THE ANTHROPOMETRIC AND METABOLIC PROFILE BETWEEN PATIENTS WITH IMPAIRED FASTING GLYCEMIA AND IMPAIRED GLUCOSE TOLERANCE ?

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Abstract

Background and Aims: *Prediabetes, a category of incipient hyperglycemia that includes impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT), has an increasing incidence in the modern world. We searched for differences in anthropometric and metabolic characteristics between subjects with isolated IFG and IFG+IGT.* ***Material and Methods:*** *In our cross-sectional study, 154 subjects with IFG and IFG+IGT, without any other major pathologies, were analyzed. Anthropometric data, lipid profile, uric acid, insulin resistance indexes, adiponectin, leptin and leptin-to-adiponectin ratio were compared.* ***Results:*** *Only 122 subjects (64 with isolated IFG and 58 with IFG+IGT), without any other identifiable major disease, were included in the final analysis. Most characteristics of the two groups were similar, only minor differences in anthropometric data, biochemical profile and insulin resistance indexes being noted. Insulin resistance indexes were stronger associated with adiponectin in the group with isolated IFG and with leptin and leptin-to-adiponectin ratio in the IFG+IGT group.* ***Conclusions:*** *Our data suggest a similar anthropometric and metabolic profile in subjects with isolated IFG and with IFG+IGT. In isolated IFG, insulin resistance seems to correlate better with adiponectin, while in IFG+IGT it seems to associate mostly with leptin and derived parameters.*

key words: *impaired fasting glycemia, impaired glucose tolerance, insulin resistance, adipokines*

Background and aims

Modern medicine witnesses an alarming increase in the number of patients with prediabetes [1], induced by the increased incidence of obesity in the global population. Prediabetes is defined as incipient forms of glycemic abnormalities, including impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT). Their definition is still

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controversial. Compared to the 1999 diagnostic criteria issued by the World Health Organization (WHO) for diabetes mellitus, IFG and IGT, the American Diabetes Association (ADA) lowered in 2003 the cut-off value for diagnosing IFG from 6.1 mmol/L (110 mg/dL) to 5.6 mmol/L (100 mg/dL) [2]. Debates followed for another few years, but in 2006, the International Diabetes Federation (IDF) and WHO announced in a common statement that they would still maintain the detection limit for IFG to 6.1 mmol/L (110 mg/dL), considering the lower cut-off value proposed by ADA as not entirely justified [3]. No matter what diagnostic criteria are used, current knowledge do not include a global image on the pathogeny of IFG and IGT, but only fragmentary data [4,5]. Studies to investigate the differences between patients with IFG and IGT are scarce and often marked by contradictory results.

As previously known, excess weight is characterized by abnormal anthropometric data, as well as by multiple changes in the level of insulin sensitivity and adipokines. The direct study of insulin resistance is marked by a high level of technical complexity and therefore is difficult to apply in clinical practice, but can be efficiently replaced by surrogate calculated variables deriving from only a few serum parameters. Up to this moment, researchers identified a large number of molecules secreted by the adipose cells, but only a few of these benefited from a thorough analysis as to be better understood in role and functions. Therefore, our work intended to identify the existing differences, if any, between patients with isolated IFG and those with IGT associated with IFG, regarding the anthropometric data, the lipid profile, some insulin resistance surrogate parameters (HOMA-IR and QUICKI) and two of the most known adipokines, adiponectin and leptin.

Material and method

Between November 2010 and July 2011, we screened all the patients aged 30 to 70 years that had been diagnosed with prediabetes (IFG and IGT) during the previous 6 months in the Clinical Centre of Diabetes, Nutrition and Metabolic Diseases of Iaşi. The diagnosis was based on the most recent IDF criteria. IFG was defined as fasting blood glucose (FBG) of 110 to 125 mg/dL and a 2-hour blood glucose < 140 mg/dL. IGT was defined as a FBG below 126 mg/dL and a 2-hour blood glucose of 140 to 199 mg/dL. Subjects with at least one of the following characteristics were excluded: 1. previously existing diabetes mellitus, diagnosed according to IDF/WHO criteria; 2. cardiovascular disease (other than arterial hypertension); 3. severe liver or kidney disease; 4. endocrine diseases; 5. treatment with biguanides, thiazolidinediones or lipid-lowering drugs; 6. patients who did not signed the informed consent. A total of 154 subjects were selected. The study was approved by the Ethics Committee of our university and all procedures were performed in accordance with the Declaration of Helsinki. All subjects gave their written informed consent to participate in the study.

All participants underwent general clinical examination. Height and weight in light clothing were measured following standardized procedures. Body mass index (BMI) was calculated as body weight (in kilograms) divided by square of the height (in meters). The waist circumference (WC) was measured midway between the lower rib margin and the iliac crest and the hip circumference was measured at the widest circumference over the trochanter in standing subjects after normal expiration. Waist-to-hip ratio (WHR) was calculated.

Venous blood samples were collected after an overnight fast. Samples were taken into vacuum tubes containing EDTA or a serum

separator gel. After sampling, tubes were immediately centrifuged at 3000g for 5 minutes. Routine biochemistry tests were performed in the same day; a part of serum was stored at −80°C for immunological measurements. Biochemistry tests (fasting glycemia, total cholesterol, triglycerides, high-density lipoprotein cholesterol – HDL-cholesterol, urea, creatinine, uric acid, transaminases) were determined with a Cobas Integra® 400 Plus analyzer (Roche Diagnostics Ltd., Basel, Switzerland) using absorbance photometry assays. The fasting insulin concentrations were measured using commercially available enzyme-linked immunosorbent assay kits from DiaMetra S.R.L. Milan, Italy. The adiponectin and leptin serum concentrations were measured using commercially available enzyme-linked immunosorbent assay kits from BioVendor GmbH, Heidelberg, Germany.

Based on these measurements, the following derived parameters were calculated: low-density lipoprotein cholesterol (LDL-cholesterol) = total cholesterol – HDL-cholesterol – triglycerides/5 (in cases with triglycerides under 400 mg/dL); non-HDL-cholesterol = total cholesterol – HDL-cholesterol; total cholesterol-to-HDL ratio; triglycerides-to-HDL ratio; leptin-to-adiponectin ratio (LAR). Insulin resistance was evaluated by the homeostasis model assessment (HOMA-IR), calculated as fasting insulin (FI) (microunits/mL) × FPG (mg/dL) / 405, as well as by the values of QUICKI index, calculated as 1 / (log FI + log FPG). The following cut-off points were used for biochemical variables: total cholesterol – over 200 mg/dL, HDL-cholesterol – below 40 mg/dL in men and 50 mg/dL in women, triglycerides – over 150 mg/dL, uric acid – over 7 mg/dL in men and 6 mg/dL in women.

All participants underwent resting electrocardiogram and echocardiography in order to exclude cases with previously unknown cardiovascular disease.

Statistical analysis

All previously mentioned data were centralized in a database using Microsoft Excel. Statistical analysis was performed using SPSS version 16.0 (Chicago, Illinois, USA). For descriptive statistics, discrete and continuous variables were expressed as frequencies and percentages, and means and standard deviations, respectively. Student t-test (for continuous variables) and χ^2-test (for categorical variables) were used to compare differences between subjects with isolated IFG and IFG+IGT; the degrees of freedom (DF) are mentioned in each case. Spearman correlation was used to analyse associations between variables. Because some parameters may vary differently between males and females, analysis was sometimes stratified by gender. Due to close matching of the groups, data are presented unadjusted. A two-sided p-value < 0.05 was considered as statistically significant.

Results

From the 154 subjects that signed the informed consent, 32 (20.77%) were excluded based on laboratory and imagistic results (abnormal clinical, biological, electrocardiogram or ultrasonography findings that identified the existence of previously unknown diabetes mellitus, cardiovascular, renal or hepatic disease). Therefore, we performed our analysis on the remaining 122 subjects.

Patients remaining in the study (50 men and 72 women) were aged between 30 and 70. 52.5% of them had isolated IFG (64 patients) and 47.5% had IFG+IGT (58 patients). Sex ratio was similar in the group with isolated IFG (42.2% men and 57.8% women) and the group with IFG+IGT (39.7% men and 60.3% women), without statistically significant differences (χ^2=0.01; DF=1; p=0.921). Mean age was not different in subjects with isolated IFG and with

IFG+IGT (59.06 ± 11.23 years vs. 58.91 ± 10.43 years; t=0.08; DF=120; p>0.05).

BMI ranged from 19.3 to 43.8 kg/m^2; excess weight (BMI ≥ 25 kg/m^2) was present in 82.8% of subjects. Patients with first and second degree obesity were the most numerous (32% with BMI between 30-34.9 kg/m^2 and 16.4% with BMI between 35-39.9 kg/m^2). Mean BMI values were not significantly different between subjects with isolated IFG and with IFG+IGT (30.09 ± 5.63 kg/m^2 vs. 31.73 ± 4.96 kg/m^2; t=1.71; DF=120; p>0.05). Similar data were found when analyzing the distribution of excess fat. Mean values of WC were not different in the two groups, while mean values of WHR showed statistical differences between subjects with isolated IFG and with IFG+IGT only in women but not in men (Table 1). Mean values of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and uric acid were not significantly different between subjects with isolated IFG and those with IFG+IGT both in males and females (Table 1).

Table 1. Values of anthropometric and biochemical parameters in male and female subjects with isolated IFG and IFG+IGT.

		IFG	**IFG+IGT**	
WC (cm)	Men	105.81 ± 11.76	106.14 ± 11.75	t=0.09; DF=48; p>0.05
	Women	95.33 ± 12.77	100.12 ± 12.94	t=1.58; DF=70; p>0.05
WHR	Men	1.0 ± 0.007	1.0 ± 0.07	t=0; DF=48; p>0.05
	Women	0.91 ± 0.07	0.95 ± 0.08	t=16.96; DF=70; **p<0.001**
Total cholesterol (mg/dL)	Men	206.4 ± 41.2	203.0 ± 27.0	t=0; DF=48; p>0.05
	Women	216.6 ± 58.2	207.2 ± 34.7	t=0.84; DF=70; p>0.05
HDL-cholesterol (mg/dL)	Men	46.59 ± 11.82	48.13 ± 14.69	t=0.40; DF=48; p>0.05
	Women	50.66 ± 14.65	50.96 ± 13.16	t=0.09; DF=70; p>0.05
LDL-cholesterol (mg/dL)	Men	126.50 ± 40.83	124.25 ± 35.52	t=0.21; DF=48; p>0.05
	Women	137.95 ± 50.12	127.53 ± 30.62	t=1.07; DF=70; p>0.05
Triglycerides (mg/dL)	Men	160.11 ± 83.77	166.78 ± 102.99	t=0.25; DF=48; p>0.05
	Women	150.45 ± 97.20	143.54 ± 63.81	t=0.47; DF=70; p>0.05
Uric acid (mg/dL)	Men	6.18 ± 1.04	6.37 ± 1.65	t=0.48; DF=48; p>0.05
	Women	4.76 ± 1.22	5.20 ± 1.54	t=1.34; DF=70; p>0.05

Table 2. Prevalences of elevated values of WC and WHR in subjects with isolated IFG and with IFG+IGT.

		Elevated WC		**Elevated WHR**	
IFG	Men	88.88% (n = 27)	χ^2=0.07; DF=1; p=0.795	77.77% (n = 27)	χ^2=0.03; DF=1; p=0.853
	Women	83.33% (n = 36)		81.25% (n = 32)	
IFG+ IGT	Men	90.47% (n = 21)	χ^2=0.16; DF=1; p=0.693	66.66% (n = 18)	χ^2=1.46; DF=1; p=0.227
	Women	91.17% (n = 34)		85.29% (n = 34)	
Men	IFG	88.88% (n = 27)	χ^2=0.09; DF=1; p=0.766	77.77% (n = 27)	χ^2=0.23; DF=1; p=0.630
	IFG+IGT	90.47% (n = 21)		66.66% (n = 18)	
Women	IFG	83.33% (n = 36)	χ^2=0.39; DF=1; p=0.534	81.25% (n = 32)	χ^2=0.38; DF=1; p=0.537
	IFG+IGT	91.17% (n = 34)		85.29% (n = 34)	

In both groups with isolated IFG and with IFG+IGT, abnormal values of WC and WHR had very high prevalences, with no differences between males and females (Table 2).

Prevalence of hypercholesterolemia was high and without differences neither between males and females in each of the two groups, nor between subjects of the same sex in each of the groups with isolated IFG and with IFG+IGT. The low values of HDL-cholesterol had significantly different prevalences between men and women only in subjects with isolated IFG, but not in those with IFG+IGT; no significant differences were noticed between subjects of the same sex in the groups with isolated IFG and with IFG+IGT (Table 3).

Mean values of non-HDL-cholesterol, cholesterol-to-HDL ratio and triglycerides-to-HDL ratio were not significantly different between subjects with isolated IFG and with IFG+IGT (non-HDL-cholesterol: 163.19 ± 52.40 mg/dL vs. 155.69 ± 33.81 mg/dL, t=0.95, DF=120, p>0.05; cholesterol-to-HDL ratio: 4.63 ± 1.67 vs. 4.35 ± 1.14, t=1.09, DF=120, p>0.05; triglycerides-to-HDL ratio: 3.81 ± 3.43 vs. 3.54 ± 2.95, t=0.47, DF=120, p>0.05).

Table 3. Prevalences of abnormal values of total cholesterol and HDL-cholesterol in subjects with isolated IFG and with IFG+IGT.

		Hypercholesterolemia		**Low values of HDL-cholesterol**		**Hypertriglyceridemia**	
IFG	Men	66.66% (n = 27)	χ^2=0.29; DF=1; p=0.587	25.92% (n = 27)	χ^2=3.98; DF=1; **p=0.046**	40.74% (n = 27)	χ^2=0.04; DF=1; p=0.845
	Women	56.75% (n = 37)		54.05% (n = 37)		35.13% (n = 37)	
IFG+ IGT	Men	56.52% (n = 23)	χ^2=0.11; DF=1; p=0.746	30.43% (n = 23)	χ^2=1.71; DF=1; p=0.191	43.47% (n = 23)	χ^2=0.01; DF=1; p=0.918
	Women	51.42% (n = 35)		51.42% (n = 35)		45.71% (n = 35)	
Men	IFG	66.66% (n = 27)	χ^2=0.20; DF=1; p=0.657	25.92% (n = 27)	χ^2=0.13; DF=1; p=0.723	40.74% (n = 27)	χ^2=0.01; DF=1; p=0.927
	IFG+IGT	56.52% (n = 23)		30.43% (n = 23)		43.47% (n = 23)	
Women	IFG	56.75% (n = 37)	χ^2=0.05; DF=1; p=0.828	54.05% (n = 37)	χ^2=0.05; DF=1; p=0.824	35.13% (n = 37)	χ^2=0.45; DF=1; p=0.500
	IFG+IGT	51.42% (n = 35)		51.42% (n = 35)		45.71% (n = 35)	

There were no significant differences in the prevalences of hyperuricemia between males and females in each of the two groups: isolated IFG – 22.22% (n = 27) vs. 10.81% (n = 37), χ^2=0.80, DF=1, p=0.372; IFG+IGT – 26.08% (n = 23) vs. 34.28% (n = 35), χ^2=0.14, DF=1, p=0.711. When comparing prevalences of hyperuricemia in subjects of the same sex in each of the groups with isolated IFG and with IFG+IGT, significant differences were noticed in females (χ^2=4.46, DF=1, p=0.035), but not in males (χ^2=0.10, DF=1, p=0.750).

Slight correlations between BMI and the values of total and LDL-cholesterol were found only in subjects with IFG+IGT (total cholesterol: r = +0.24, LDL-cholesterol: r = +0.19), while no correlation was observed in subjects with IFG (total cholesterol: r = +0.01, LDL-cholesterol: r = -0.08). WHR appeared to have only slight correlations with the values of total and LDL-cholesterol, negative in the case of subjects with isolated IFG (total cholesterol: r = -0.15, LDL-cholesterol: r = -0.16) and positive in subjects with IFG+IGT (total cholesterol: r = +0.19, LDL-cholesterol: r = +0.14). HDL-cholesterol showed only a slight negative correlation with BMI in subjects with isolated IFG (r = -0.24), while no correlation with BMI was identified in subjects with IFG+IGT (r = -0.08). In both groups with isolated IFG and IFG+IGT, HDL-cholesterol had a slight negative correlation with the values of WHR (r = -0.26 and r = -0.14). Triglycerides had slight positive correlations with BMI and WHR both in patients with isolated IFG (BMI: r = + 0.34, WHR: r = + 0.14) and IFG+IGT (BMI: r = +0.10, WHR: r = +0.19). Uric acid also had positive correlations with BMI and WHR both in patients with isolated IFG (BMI: r = +0.33, WHR: r = +0.47) and IFG+IGT (BMI: r = +0.28, WHR: r = +0.21).

Insulin resistance parameters and adipokines had, in most cases, similar values between the two groups (Table 4); the only statistical difference was observed in QUICKI values,

which was not accompanied, however, by similar differences in HOMA-IR values.

In patients with isolated IFG, HOMA-IR and QUICKI values correlated both with adiponectin and leptin, but not with LAR. In patients with IFG+IGT, these insulin resistance indexes showed correlations with adiponectin only for QUICKI, but not for HOMA-IR, while both of them correlated with leptin and LAR (Table 5).

Table 4. Insulin resistance parameters and adipokine levels in patients with isolated IFG and IFG+IGT.

Parameter	IFG	IFG+IGT	Statistical significance
HOMA-IR	1.44 ± 1.55	1.94 ± 1.74	t=1.67; p>0.05
QUICKI	0.63 ± 0.07	0.59 ± 0.08	t=2.93; **p=0.01**
Adiponectin (ng/ml)	11450 ± 4678	11738 ± 4801	t=0.33; p >0.05
Leptin (ng/ml)	17.28 ± 14.74	22.47 ± 16.20	t=1.04; p >0.05
LAR (mg/g)	2.16 ± 3.56	2.15 ± 2.05	t=0.02; p>0.05

Table 5. Correlations of insulin resistance indexes with adipokine profile in patients with isolated IFG and IFG+IGT.

		Isolated IFG		IFG+IGT	
		HOMA-IR	**QUICKI**	**HOMA-IR**	**QUICKI**
Adiponectin	r-value	**-0.374**	**0.442**	-0.167	**0.280**
	P-value	**0.002**	**0.0001**	0.210	**0.033**
	n	64	63	58	58
Leptin	r-value	**0.263**	**-0.362**	**0.415**	**-0.440**
	P-value	**0.038**	**0.004**	**0.001**	**0.001**
	n	63	63	57	57
LAR	r-value	0.221	-0.248	**0.350**	**-0.381**
	P-value	0.082	0.050	**0.008**	**0.003**
	n	63	63	57	57

Discussions

The large proportion of patients (20.77%) that were identified with diabetes mellitus, cardiovascular, renal or hepatic disease is an alarming finding in a population previously considered as having a good state of health. The design of this study imposed limits that did not allow us to further analyze the etiology of these health issues, as to find if, for example, the hepatic disease might have a metabolic cause or the renal disease – an atherosclerotic one.

The comparison between subjects with IFG and IGT was rarely performed by medical researchers in the last years. This analysis can therefore contribute to the detection of differences or similarities between incipient fasting and postprandial hyperglycemia.

When analyzing the anthropometric data, we found the majority of patients (48.4%) to have first or second degree obesity, while fewer had a BMI over 40 kg/m^2. These findings might have multiple explanations. First, the large number of obese patients can be attributed to the fact that increased values of BMI associate with increased levels of insulin resistance and therefore with an increased risk of dysglycemia. Second, the lower number of cases with third degree obesity might be explained by speculating that such patients feature a greater risk of already having diabetes, which would have excluded them from our analysis. As to increased values of WC and WHR, we must emphasize their high prevalence both in men and women with isolated IFG and with IFG+IGT, most probably explained by the close association prediabetic dysglycemia has with abdominal obesity [5], as both conditions are associated with elevated circulating concentrations of free fatty acids, oxidative stress, mitochondrial dysfunction, disordered

nitric oxide release and endothelial dysfunction, all leading to insulin resistance [6].

Our data showed a high prevalence of hyperuricemia and lipid profile anomalies in both groups with isolated IFG and IFG+IGT. This is not a surprising result, given the known associations between prediabetes and these biochemical changes [7]. When the groups with isolated IFG and IFG+IGT were compared, most of the anthropometric and biochemical results were found to have similar mean values. As most studies up to this moment concentrated only on the comparison between normoglycemic, prediabetic and/or type 2 diabetic subjects [8,9], our paper adds knowledge to a chapter not yet sufficiently explored. Our findings add to data from other studies, which found no difference between subjects with isolated IGT and isolated IFG [10], but contradicts results other authors published recently, where BMI, WC, total, HDL and non-HDL-cholesterol, triglycerides and triglycerides-to-HDL ratio presented differences that argued for a more unfavorable cardiovascular risk profile in subjects with IFG+IGT than in those with isolated IFG (which they found to be close to normal controls) [4]. These differences, if confirmed by other future studies, might be explained by the distinct sites insulin resistance has in the two categories of incipient hyperglycemia – the liver in isolated IFG (with a normal insulin sensitivity in muscle) and both the liver and the muscle in IFG+IGT category. On the other hand, our study was performed on groups with similar age and sex ratio (which is not the case in the other publication) and the identification of subjects with isolated IFG was made using fasting glycemic levels ≥ 110 mg/dL, according to WHO/IDF guidelines [3], and not ≥ 100 mg/dL, as the other authors preferred to do according to ADA guidelines [11], which might have contributed to selecting patients with more pronounced metabolic anomalies, and therefore with similar characteristics to those that also have postprandial glycemic changes. Moreover, other studies identified pathological changes in the HDL-cholesterol subclasses even from the IFG phase [12], so anomalies in the lipid profile might exist even with early dysglycemic changes.

Regarding uric acid, studies performed so far have concentrated mostly on its relationship with diabetes [13-16]. There are only a few analyses to evaluate the relationships, if any, between uric acid and different stages of incipient hyperglycemia [17,18]. In our female subjects, prevalence of hyperuricemia was different between the groups with IFG and IFG+IGT, but this difference disappeared in male subjects. This result supports data recently published by German researchers, who also found a stronger association of uric acid with isolated IFG and IFG+IGT in females than in males [19].

As to the relations between anthropometric data, lipid profile and uric acid, the strongest correlations to be identified, in both groups with isolated IFG and with IFG+IGT, were those between BMI and WHR as compared to triglycerides and uric acid. One plausible explanation is that these two biochemical parameters – considered as components of the metabolic syndrome – might have an increasing trend in subjects with an excess fat mass (which also implies higher values of BMI and WHR), which tend to be more insulin resistant. Hyperuricemia, for instance, is strongly associated with insulin resistance [20], being thought to increase insulin resistance by stimulating inflammation and by leading to endothelial dysfunction and nitric oxide inhibition [21]. On the other hand, hyperinsulinism secondary to insulin resistance may reduce urate renal excretion and induce hyperuricemia [22-24]. Other studies also

reported an association between uric acid values and excess weight (especially if centrally distributed) in a population including normoglycemic obese subjects, prediabetics and type 2 diabetics [25]. Our data show that this association exists no matter if incipient dysglycemia has a fasting or a postprandial pattern. However, the present research did not take into account eating habits (although they can influence some components of the lipid profile and uric acid levels), as other studies did [26].

It is less clear why HDL-cholesterol – also known to be related to insulin resistance levels – did not constantly presented correlations of the same magnitude (although negative) with the anthropometric profile. As correlations of HDL-cholesterol with BMI and WHR were stronger in subjects with isolated IFG than in those with IFG+IGT, it would be tempting to speculate that HDL-cholesterol seems to be more influenced by the degree of the excess adiposity in the case hyperglycemia occurs in fasting conditions than if both fasting and postprandial glycemic levels are modified. Nevertheless, this conclusion must be supported by an extended analysis in larger groups of patients and longitudinal studies.

Comparison of insulin resistance indexes between subjects with isolated IFG and IFG+IGT led to similar results in our study groups when HOMA-IR was used, the only difference being noted for QUICKI. Data from the literature are conflicting, suggesting either that insulin resistance is more pronounced in IFG subjects, where it constitutes the main mechanism (while IGT is predominantly generated by defaults in insulin secretion), or that insulin resistance also plays an important role in subjects with IGT [27-29].

The few studies that investigated levels of plasma adiponectin [30-32] and leptin [33,34] in prediabetes gave contradictory results. In our subjects, no differences were identified when the mean values of adipokines were compared, which describes a similar profile of subjects with isolated IFG and IFG+IGT. Other authors consider that adiponectin is a marker for the progression of glucose intolerance in prediabetic stages [35], so we might have expected its mean values to be higher in patients with isolated IFG than in those with IFG+IGT. Nevertheless, other studies identified similar adiponectin levels in prediabetic and normoglycemic male subjects [32], suggesting that some categories of incipient dysglycemia are not necessarily accompanied by a decline in plasma adiponectin levels.

Correlations between insulin resistance indexes and adipokines were also an interesting analysis target in patients with prediabetes. As insulin resistance – known to underlie the metabolic and cardiovascular anomalies of these patients [7,36] – is difficult to estimate by direct methods, while the cost and technical difficulties of determining seric levels of adipokines are decreasing in the last years, it would be useful to identify supplementary ways to estimate decreased insulin sensitivity by means of evaluating the adipokine profile. When the relationship between insulin resistance indexes and adipokines was studied in the two groups, different correlation patterns were identified. In subjects with isolated IFG (in other words, isolated fasting dysglycemia), adiponectin seemed to have the strongest connection with insulin resistance indexes, leptin – a more limited one and LAR no connection whatsoever, while in those with IFG+IGT (influenced not only by fasting, but also by postprandial hyperglycemia) HOMA-IR and QUICKI correlated predominantly to leptin and LAR. This might be explained by speculating that postprandial metabolic anomalies are mostly linked to the variations in leptin secretion, known to modulate the appetite and energy balance, while fasting anomalies are predominantly linked to adiponectin, whose secretion is less correlated to food intake. If this

is true, then the study of insulin resistance should be made by means of dosing different adipokines in subjects with isolated IFG and IFG+IGT. In other studies on prediabetic subjects (which did not separate, however, subjects with isolated IFG from those with IFG+IGT) adiponectin was found not to be associated with HOMA-IR [32], without a clear explanation, while leptin was found to be associated with insulin resistance [34]. It is possible that our hypothesis explained, at least partially, these apparently conflicting findings. Moreover, our data support other findings which assert that IFG and IGT are associated with distinct adipokine patterns, reflecting the pathophysiological differences that underlie these two incipient hyperglycemic states [33,37]. The connection between leptin and insulin resistance seems to be a bidirectional one, given the fact that leptin inhibits insulin synthesis and secretion, while insulin stimulates leptin secretion [38].

One of the limitations of our study is that a temporal or a causal relationship between insulin resistance indexes and adipokine profile were impossible to demonstrate due to the cross-sectional design of the study. Moreover, being an observational research, it cannot rule out the possibility that unmeasured or residual confounding factors might contribute to the observed or missing associations. Another limit of our study is that it did not include a group of subjects with isolated IGT; however, the identification of such patients would have supposed an extended screening in the normoglycemic population (using OGTT), which would have constituted a very important financial effort that even international organizations do not advise to be performed regularly. Finally, another possible limit of our data is that insulin resistance was not measured by clamp techniques, but using surrogate parameters (HOMA-IR and QUICKI). On the other hand, the study has several strengths, as it includes a relatively homogenous population and – by focusing on prediabetes subjects instead of diabetic patients – it excludes some confounding factors such as drug treatment effect and decreased β-cell function within diabetic individuals, both having a direct effect on circulating insulin levels. Our research should be extended on larger study groups, optimally including subjects with normal glucose tolerance as controls and maybe even newly diagnosed (and not yet treated) type 2 diabetics, in order to obtain a confirmation of our results. A further step would be the initiation of a prospective study that would allow us to follow the evolution of our prediabetic subjects and to search for a cause-effect relationship in the case of the associations identified by the present study.

Conclusions

Our data support only the existence of minor differences between subjects with isolated IFG and with IFG+IGT regarding anthropometric data, biochemical profile and insulin resistance indexes, while no difference was noted in adipokines mean values. As to the relation between anthropometric data and biochemical profile, the strongest correlations that were identified in both groups were those between body mass index and waist-to-hip ratio on one hand and triglycerides and uric acid on the other hand. In subjects with isolated IFG, insulin resistance indexes seemed to have the strongest connection to adiponectin, while in those with IFG+IGT they appeared to be better correlated to leptin and leptin-to-adiponectin ratio.

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