Impact of plasmatic lipids in glycemic control and its influence in the cardiometabolic risk in morbidly obese subjects

Impacto dos lipídios plasmáticos no controle glicêmico e sua influência no risco cardiometabólico em pacientes obesos mórbidos

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ABSTRACT

Objectives: To evaluate whether biochemical parameters are associated with a good glycemic control and to identify the occurrence of cardiometabolic risk variables. **Material and methods:** One hundred forty Brazilians were evaluated. The subjects were characterized with regard to glycemic control as good, fair and poor and were divided into tertiles by TG and HbA_{1c}. We use the ROC curve to determine which variables were predicted of poor glycemic control and the factor analyses to identify the domains that segregated among the risk variables. **Results:** Fasting glucose and insulin levels, TG level, VLDL-C and HOMA-IR increased significantly across HbA_{1c} tertiles. The best marker for identification of poor glycemic control was triglycerides. The presence of cardiometabolic abnormalities did not alter the glycemic control, but HOMA-IR was significantly higher in subjects with abnormalities. **Conclusion:** The use of TG levels offers a reasonable degree of clinical utility. In morbidly obese subjects insulin resistance is associated with individual cardiometabolic factors. Arq Bras Endocrinol Metab. 2009;53(6):747-54

Keywords

Obesity; blood glucose; bariatric surgery; *diabetes mellitus*

RESUMO

Objetivos: Avaliar o quanto os lipídios plasmáticos, o IMC e a glicemia de jejum estão associados com um bom controle glicêmico e identificar a ocorrência de variáveis do risco cardiometabólico. **Método:** Cento e quarenta brasileiros foram avaliados. Os pacientes foram caracterizados, de acordo com o controle glicêmico, como tendo bom controle, moderado controle e controle ruim e foram divididos em tercis de TG e HbA_{1c}. Utilizou-se a curva ROC para determinar quais variáveis predizem um controle glicêmico inadequado e a análise fatorial para identificar os domínios que segregam as diferentes variáveis. **Resultados:** A glicemia de jejum e os níveis de insulina, os níveis de TG, VLDL-C e HOMA-IR aumentaram significativamente de acordo com os tercis de HbA_{1c}. O melhor marcador para identificação de indivíduos com um controle glicêmico ruim foi o triglicérides. A presença de anormalidades cardiometabólicas não alterou significativamente o controle glicêmico, mas o HOMA-IR foi significativamente maior nestes indivíduos. **Conclusão:** O uso dos níveis de TG oferece uma boa utilidade clínica. Em pacientes obesos mórbidos, a resistência à insulina esta associada com fatores de risco cardiometabólico. AArq Bras Endocrinol Metab. 2009;53(6):747-54

Descritores

Obesidade; glicemia; cirurgia bariátrica; diabetes melito

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INTRODUCTION

The diabetic complications can be prevented or delayed by tight glycemic control. The American Diabetes Association (ADA) recommend HbA_{1c} less than 7% as glycemic goal for non-pregnant diabetic pacients (1). Even in patients who cannot achieve the goal,

improved glycemic control is still associated with decreased rates of microvascular complications (2-3). In obese patients, the presence of type 2 diabetes (DM2) is a major risk factor for cardiovascular diseases and the impaired glucose tolerance (IGT) is considered to be an independent risk factor for macrovascular complications (4). Thus, in morbidly obese patients, the glycemic control has to be more intensive.

Glycemic control depends mainly on the degree of residual pancreatic beta-cell function and insulin sensitivity (5). A number of clinical features are associated with these two factors, such as body mass index (BMI), waist circumference, plasma triglycerides as well as HDL-cholesterol, all factors related to insulin resistance (6). In one investigation, McLaughlin and cols. found that in subjects with a BMI of 25 kg/m^2 or more, the lipid criteria, specifically triglycerides (TG) levels and TG-HDL-C ratio, were sensitivity markers of insulin resistance (7). They found that the cut offs for the lipid criteria that were most predictive of insulin resistance were TG level of 130 mg/dL or more and/or TG-HDL-C ratio of 3 or more.

The cardiometabolic risk encompasses a cluster of modifiable classic and emerging risk factors and markers that identify individuals at increased risk for cardiovascular disease and type 2 diabetes (8). It includes the factors that make up the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) definition of metabolic syndrome and encompasses four additional factors: smoking, elevated LDL-C, inflammatory markers and insulin resistance (8-9). In a classical study, Meigs and cols. identified three factors underlying the clustering of certain risk variables. The first cluster includes insulin levels, triglycerides and HDL-C levels, BMI and waist-to-hip ratio, all of which were associated with metabolic syndrome. The second cluster includes glucose and insulin levels which are associated with impaired glucose tolerance. The third cluster includes systolic and diastolic blood pressure and BMI, factors that are associated with hypertension (10).

The primary purpose of the present study was to evaluate whether plasmatic lipids, BMI and fasting glucose are associated with a good glycemic control. In the secondary aim of this study, we investigated the occurrence of cardiometabolic risk variables, the distribution of insulin resistance and its association with the individual cardiometabolic risk variables and how cardiometabolic risk factors cluster and how much of such clustering may be associated with insulin resistance in morbidly obese subjects.

METHODS

Study population

One hundred and forty Brazilians (29 men and 111 women), with a mean age of 34 ± 8 years and a mean BMI of 45 ± 4 kg/m^2 were evaluated. Patients on insulin treatment, as well as those with liver or kidney disease and diabetes mellitus type 1 were excluded. Blood samples were drawn in the morning after an overnight fast (minimum of eight hours) and the biochemical parameters were analyzed as the standard. Insulin resistance was calculated using the homeostasis model assessment (11). The subjects were characterized with regard to glycemic control as good (HbA_{1c} < 7%, n = 42), fair (HbA_{1c} 7 to 8%, n = 64) and poor (HbA_{1c} > 8%, n = 34). To assess the effect of weight loss in cardiometabolic risk, the patients underwent laparoscopic Roux-en-Y gastric bypass (RYGBP), and after eight months all the tests were repeated. All procedures were carried out at Faculdade de Medicina do ABC (FMABC) and affiliated institutions.

The normal cut off values for anthropometric, lipid and blood pressure parameters used in this study was the criteria used by the International Diabetes Federation: waist circumference ≥ 94 cm in men, ≥ 80 cm in women or BMI ≥ 30 kg/m^2; triglycerides levels ≥ 150 mg/dL (1.7 mmol/L) and/or specific treatment; HDL-C levels < 40 mg/dL (1 mmol/L) in men, < 50 mg/dL (1.3 mmol/L) in women and/or specific treatment; fasting glucose (FG) ≥ 100 mg/dL (5.6 mmol/L) and/or DM2 patient; systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg and/or specific treatment (9). The patients were divided into tertiles by TG and HbA_{1c}; these tertiles were, respectively: 512 to 150; 10.9 to 7.7, 148 to 105; 7.6 to 7 and 104 to 43 mg/dL; 6.9 to 5.4%.

Statistical analysis

Data are presented as mean ± SD. Because results did not vary when adjusted for sex, combined results were presented. Linear regression and stepwise multiple regression analyses were performed to evaluate the relationship among HbA_{1c}, plasmatic lipids, BMI and fasting glucose levels. Tertile distributions of the patients were compared by 1-way analysis of variance (ANOVA) with Tukey corrections for multiple comparisons. Categorical data were analyzed with χ^2 test. Areas under the receiver-operating characteristics (ROC) curves

were determined for each variable to identify which were predictors of poor glycemic control. Areas under the ROC curve are provided with standard errors. An ROC curve is a plot of sensitivity (true positive) *versus* 1-specificity (false positive) for each potential marker.

Pearson's correlation coefficients were computed in order to explore the correlations between two variables. Factor analyses with principal component analyses (PCA) were used to identify the domains that segregated among the risk variables (12). The risk variables included fasting plasma glucose and insulin, HDL-C, HOMA-IR, HbA_{1c}, triglycerides, waist-to-hip ratio and BMI. PCA method with orthogonal rotation identifies subsets of clusters of correlated variables. Interpretation was based on the correlations called loadings (range -1.0 to 1.0) between the factors and the original independent variables greater than ± 0.30 to interpret the resulting factor pattern (12).

All statistical analyses were made with the statistical software package SPSS (v 15.0; SPSS, Chicago, IL), MedCalc software and ROCKIT 0.9B (Department of Radiology from The University of Chicago). Statistical significance was considered at $p < 0.05$.

RESULTS

Association between glycemic control and biochemical parameters

The tertiles of TG and HbA_{1c} were determined on the basis of the studied population of 140 individuals. Of these, for triglycerides and HbA_{1c} respectively, 45 and 42 were in the first tertile, 35 and 46 were in the second and 60 and 52 were in the third (Table 1). The HOMA-IR increased across the triglycerides tertiles and in the third tertile (upper limit) it was significantly higher than in the first tertile (inferior limit). For the

Table 1. Characteristics by triglycerides and HbA_{1c} tertiles of the subjects

	Triglycerides					
	Tertile 1 (n = 45)	p[a]	Tertile 2 (n = 35)	p[b]	Tertile 3 (n = 60)	p[c]
Age (years)	37.4 ± 10	996	37.2 ± 10	999	37.3 ± 9	998
BMI (kg/m²)	44.1 ± 4	982	43.9 ± 4	908	44.3 ± 4	967
Fasting insulin (μU/L)	13.3 ± 1	644	13.9 ± 3	466	14.6 ± 3	060
Fasting glucose (mg/dL)	92.7 ± 10	597	97.9 ± 29	413	104.3 ± 26	038*
HOMA-IR	3.0 ± 0	437	3.5 ± 2	528	3.9 ± 2	030*
HbA_{1c} (%)	6.8 ± 0	169	7.1 ± 0	000*	8.3 ± 0	000*
HDL-C (mg/dL)	47.9 ± 12	685	45.9 ± 9	714	47.7 ± 10	994
% metabolic syndrome	44.4	033*	57.1	712	60	003*
% lipid criteria	44.4	000*	68.6	000*	100	000*
	HbA_{1c}					
	Tertile 1 (n = 42)	p[a]	Tertile 2 (n = 46)	p[b]	Tertile 3 (n = 52)	p[c]
Age (years)	36.3 ± 10	941	35.6 ± 9	120	39.6 ± 10	252
BMI (kg/m²)	43.9 ± 4	896	43.5 ± 3	302	44.8 ± 4	586
Fasting insulin (μU/L)	12.4 ± 1	146	13.5 ± 1	000*	15.8 ± 3	000*
Fasting glucose (mg/dL)	84.8 ± 7	093	94 ± 9	000*	114.7 ± 31	000*
HOMA-IR	2.6 ± 0	232	3.1 ± 0	000*	4.7 ± 2	000*
TG (mg/dL)	97 ± 32	093	125.5 ± 37	000*	231.8 ± 93	000*
TG-HDL-C ratio	3.3 ± 1	903	3.6 ± 2	993	3.5 ± 2	940
HDL-C (mg/dL)	49.7 ± 11	644	47.6 ± 11	523	45.2 ± 9	120
VLDL-C (mg/dL)	24.6 ± 11	517	27.3 ± 9	000*	41.7 ± 13	000*
LDL-C (mg/dL)	111.3 ± 36	176	125.5 ± 35	965	127.4 ± 39	095
% metabolic syndrome	54.8	057	47.8	047*	59.6	062
% lipid criteria	47.6	000*	78.3	003*	92.3	000*

* $p < 0.05$.
[a] Between T1 and T2 (0.); [b] Between T2 and T3 (0.); [c] Between T1 and T3 (0.).

HbA_{1c} group, fasting glucose and insulin levels, TG level, VLDL-C and HOMA-IR increased significantly across tertiles.

The sensitivity, specificity and positive likelihood ratio (+LR) value of the metabolic syndrome to diagnose poor glycemic control in Brazilians were 45%, 54.7% and 1.02% respectively. For the lipid criteria, the sensitivity, specificity and + LR to identify individuals with poor glycemic control were, respectively, 85%, 52% and 1.8%.

The Figure 1 shows the ROC curve for all potential metabolic markers evaluated. The best markers for identification of individuals with poor glycemic control were, in rank-ordered, triglycerides, fasting glucose and fasting insulin, and the AUC of these markers were significantly greater than those of the other three markers (Table 2). The sensitivity and the specificity for these markers were, respectively, 62, 63 and 36% and 97, 88 and 100%.

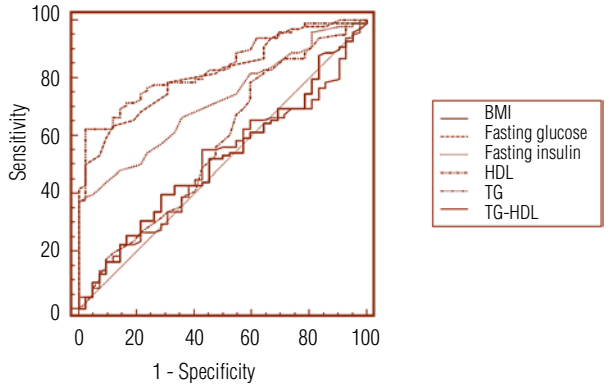

Figure 1. Receiver-operating characteristic curves for metabolic markers of poor glycemic control.

Table 2. Comparison of areas under ROC curves (AUC) for parameters that are potentials markers of poor glycemic control

Variable	AUC (Mean ± SE)	95% Confidence interval
BMI	0.518 ± 0.05	0.432 – 0.603
Fasting glucose	0.815 ± 0.03	0.741 – 0.876
Fasting insulin	0.719 ± 0.04	0.637 – 0.792
HDL-C	0.571 ± 0.05	0.485 – 0.654
Triglycerides	0.837 ± 0.03	0.765 – 0.894
TG-HDL-C Ratio	0.505 ± 0.05	0.419 – 0.590

To test these results, the relative ability of the cut off values found for the triglycerides, fasting glucose and insulin were compared in order to identify individuals with good or poor glycemic control. It can be seen, in Table 3, that a high TG level (> 146 mg/dL) identified 62.2% of the individuals with poor glycemic control (PGC), and a low TG (≤ 146 mg/dL) identified 95.2% of the individuals with good glycemic control (GGC) ($\chi^2 = 39.2$, $p < 0.0001$). Similarly, a high fasting glucose level correctly identified 65.3% of the patients with PGC, and a low FG identified 81% of the patients with GGC ($\chi^2 = 25.1$, $p < 0.0001$). Quite the opposite, high levels of fasting insulin identified only 38.8% of individuals with PGC, but the low levels correctly identified 97.6% of individuals with GGC ($\chi^2 = 19.3$, $p < 0.0001$).

HbA_{1c} was significantly correlated with fasting glucose and insulin levels, triglycerides level, HOMA-IR and HDL-C level (Pearson's correlation coefficients = 0.709, 0.652, 0.707, 0.694 and -0.398, respectively). To assess the relative contribution of these parameters in the prediction of HbA_{1c}, we performed multiple stepwise linear regression analyses with HbA_{1c} as dependent variable and FG, FI, TG, HOMA-IR, HDL-C and BMI as the independent variables. The results of these analyses indicated that, in the regression model, both FG and TG significantly predicted HbA_{1c} (FG, $\beta = 0.29$, $p < 0.0001$; TG, $\beta = 0.21$, $p < 0.0001$). The others parameters did not significantly contribute to the model.

Assessment of cardiometabolic risks

We found that, before RYGBP, 14.2% of the subjects could be include in all of the three physiologic domains of the insulin resistance syndrome and, after the surgery, this prevalence down to 7.1% ($p < 0.05$). Thus, before the surgery, only 10.7% of the patients had none factor and, after the procedure, this number increased to 27.1% ($p < 0.05$) (Table 4).

The prevalence of cardiometabolic risk factors is shown in Table 5. Median values of HOMA-IR were significantly higher in subjects with abnormal values for

Table 3. Ability of triglycerides, fasting glucose and fasting insulin to identify individuals with poor or good glycemic control

	TG 146	TG > 146	FG < 92	FG > 92	FI < 15.3	FI > 15.3
PGC (n = 98)	37 (37.8%)	61 (62.2%)	34 (34.7%)	64 (65.3%)	60 (61.2%)	38 (38.8%)
GGC (n = 42)	40 (95.2%)	2 (4.8%)	34 (81%)	8 (19%)	41 (97.6%)	1 (2.4%)

TG: triglycerides (mg/dL); FG: fasting glucose (mg/dL); FI: fasting insulin (μU/L); PGC: poor glycemic control ($HbA_{1c} > 7\%$); GGC: good glycemic control ($HbA_{1c} \leq 7\%$).

each parameter, except in the HDL and in the smokers group. The presence of cardiometabolic abnormalities did not altered significantly the glycemic control, only in the LDL group. In the triglycerides and in the fasting glucose group, the relationship approach's significance ($p = 0.073$ and $p = 0.191$, respectively).

Principal axis factor analysis with varimax rotation was conducted to assess the underlying structure for six parameters. We identified two dominant factors that explained 56.1% of the total variance of data. After rotation, the first and the second factors accounted for 32.97 and 23.13% of the variance, respectively (Table 6). In the first factor, called glucose factor, fasting glucose and insulin levels had positive loadings. In the second factor, called lipid factor, LDL-C and triglycerides had positive loading and HDL had negative loading. Lipid profile was linked to the glucose factor by shared correlations with fasting glucose.

Table 4. Prevalence of physiological domains of the insulin resistance syndrome, before and after RYGBP, based on the study by Meigs and cols. (10)

	Before	After	p
None	15 (10.7%)	38 (27.1%)	< 0.05
Factor one only[a]	53 (37.8%)	56 (40%)	> 0.05
Factor two only	0 (0%)	1 (0.7%)	> 0.05
Factor three only	16 (11.4%)	11 (7.8%)	> 0.05
Factor one and three	30 (21.4%)	16 (11.4%)	< 0.01
Factor one and two	6 (4.2%)	8 (5.7%)	> 0.05
Factor one, two and three	20 (14.2%)	10 (7.1)	< 0.05

No (0%) individuals were classified as indeterminate (factor two and three).

[a] To estimate prevalence, the factor one was defined as the presence of at least two of the three characteristics: hiperinsulinemia (a fasting insulin level exceeding the 90th percentile of its distribution among subjects with normal glucose tolerance), dyslipidemia (either a low HDL-C or an elevated triglyceride level) or obesity (either central or BMI ≥ 30 kg/m²).

Table 5. Prevalence of cardiometabolic abnormalities and values of HOMA-IR and HbA1c in relation to presence of abnormalities

	Prevalence	HOMA-IR (SI) (Mean ± SD)		HbA_{1c} (%) (Mean ± SD)	
		Presence	Absence	Presence	Absence
HDL-C[a]	80 (57.1%)	3.55 ± 2.0	3.64 ± 1.5	7.59 ± 1.1	7.50 ± 1.1
Triglycerides[a]	60 (42.9%)	3.98 ± 2.0	3.29 ± 1.5*	7.75 ± 1.1	7.41 ± 1.0
Hypertension[a]	66 (47.1%)	4.05 ± 2.0	3.17 ± 1.4*	7.55 ± 1.0	7.55 ± 1.1
Fasting glucose[a]	43 (30.7%)	5.62 ± 2.1	2.68 ± 0.3*	7.37 ± 0.9	7.64 ± 1.1
Smoking	98 (70%)	3.59 ± 1.8	3.48 ± 1.5	7.56 ± 1.1	7.46 ± 1.0
LDL-C[b]	103 (73.6%)	3.81 ± 1.9	2.95 ± 1.1*	7.69 ± 1.1	7.17 ± 1.0*

[a] Abnormal cut offs according to IDF criteria (see "Methods" section).

[b] Abnormal cut off: LDL-C > 100 mg/dL.

* $p < 0.05$ for the difference between presence or absence.

Table 6. Factor loading patterns after orthogonal rotation of principal components showing the clusters of cardiometabolic risk variables

	Factor loading		Communality
	1	2	
Fasting glucose	0.887	0.304	0.76
Fasting insulin	0.907		0.76
HDL-C		-0.513	0.57
LDL-C		0.543	0.58
Triglycerides		0.600	0.57
Eigen values	3.928	2.314	
% of variance	32.97	23.13	

Loadings < 0.30 are omitted.

DISCUSSION

Association between glycemic control and biochemical parameters

In the next century more than 100,000,000 individuals will be obese and, of these, more than 15,000,000 will become diabetic. The mechanism through which obesity causes diabetes remains obscure, but it is known that obesity is associated with insulin resistance, and that effective compensatory hiperinsulinemia initially maintains blood glucose levels within normal range (13). However, after some time, the ability of pancreatic β cells to compensate for increasing insulin resistance may flag, the so-called β-cell failure.

Obesity, as well as diabetes, is associated with dyslipidemia, characterized by an increase in circulating free fatty acids (FFA), accumulation of triglycerides in peripheral tissues and changes in lipoprotein profile (13-16). High plasma levels of FFA are related with excessive accumulation of fat in pancreatic β-cell, and it leads to cellular dysfunction, called lipotoxicity (17-19). The lipotoxicity is the result of a constellation of islet derangements, like the decreased β-cell GLUT-2 expression (20), enhanced nitric oxide formation (21), impaired β-cell function (20) and apoptosis of a substantial subgroup of β cells (18).

In our results, a high level of triglycerides (upper tertile) was associated with insulin resistance (Table 1), a known fact, and with a poor glycemic control (Figure 1 and Tables 1, 2 and 3). Like said before, the glycemic control depends mainly on the degree of residual pancreatic beta-cell function and insulin sensitivity (5), and the TG is associated with both. The pancreatic islets exhibit an increased incorporation of [^{3}H]palmitate into triglycerides, and this is believed to be a major factor in the overaccumulation of fat, given the high levels of circulating fatty acids and triglycerides that characterizes obesity (22-23). A normal pancreatic islet contains approximately 24 ng of triglycerides and this number can increase to 990 ng in the islets of obese, leptin-resistance Zucker diabetic fatty rats (24), the animal model used to study the mechanisms of β-cell failure in obesity.

In our study, a poor glycemic control was associated with high levels of VLDL-C and LDL-C and with a low level of HDL-C too (Table 1). It was demonstrated that purified human very low-density lipoprotein and low-density lipoprotein particles reduced insulin mRNA levels and β-cell proliferation and were proapoptotic, whereas high-density lipoprotein protected β-cells against these proapoptotic effects. These protective effects were mediated, at least partially, by inhibition of caspase-3 cleavage and activation of Akt/protein kinase B, whereas proapoptotic lipoproteins seem to act via c-Jun N-terminal kinase (25). These results are highly suggestive that the changes in lipoprotein profile observed in obesity could contribute to the pathogenesis and progression of β-cell failure (14).

Other proposed pathway of lipotoxicity is the enhanced expression of sterol regulatory element-binding protein-1c (SREBP-1c) and lipogenic genes such as fatty acid synthase (FAS) and acetyl-coenzyme A carboxylase (ACC) in pancreatic islets of ZDF rats (26). The SREBP-1c, through a direct interaction with *cis*-acting element, regulate the expression of the uncoupling protein-2 (UCP-2), which has the SRE sequence on its promoter region. It has been shown that the expression of UCP-2, which has been involved in dissipation of the mitochondrial proton gradient, was enhanced in the pancreatic islets of lipotoxicity models (15).

In obesity, the flux of FFA from adipocytes into islets is greatly enhanced in proportion to the obesity. Because leptin levels, which are known for their ability to lower the TG content of isolated islets by reducing esterification and by increasing oxidation of FFA, also rise proportionately to the obesity, it is suggested that they prevent excessive accumulation of triglycerides and lipotoxicity. However, if the islet leptin receptors are defective or the sensitivity of islets to leptin is diminished by postereceptor defects, like in morbid obesity, islet fat content may rise to a lipotoxic level, in which case adipogenic diabetes will ensue (19).

The obesity is also associated with a pro-inflammatory status that provides a potential link between insulin resistance and endothelial and beta cell dysfunction. The visceral and subcutaneous adipose tissues are the major source of cytokines/adipokines, which are low molecular weight proteins that participate in inflammation and immune response. Thus, increased adipose tissue mass is associated with alteration in adipokine production as over expression of tumor necrosis factor α, plasminogen activator inhibitor 1 and interleukin 6 (14).

In summary, the role of plasmatic lipids in glycemic control is well established. We believe that the results shown in Tables 2 and 3 demonstrate that the use of TG levels and fasting insulin and glucose levels offer a reasonable degree of clinical utility. Of these alternatives, the plasma triglycerides levels are the metabolic

markers most closely related to poor glycemic control. In addition, this marker is said to increase CVD (27) risk as well as to be associated with insulin resistance (28). Thus, if the goal is to identify those insulin-resistant with poor glycemic control individuals who are at risk for CVD, this marker may offer some advantage over the others.

Assessment of cardiometabolic risks

In this population-based study, we found that, before RYGBP, 78.5% of morbidly obese patients had at least one cardiometabolic risk factor, and that these factors clustered into two groups. The atherogenic dyslipidemia (high TG and low HDL-C) is the commonest cardiometabolic abnormalities. In this population, the BMI is higher than the normal weight population and relatively constant, hence, the obesity did not constitute an important factor in our patients. The central characteristics of a unified metabolic syndrome included hyperglycemia (reflecting insulin resistance) and dyslipidemia. The glucose intolerance was linked to the dyslipidemia through mutual associations with fasting glucose levels.

Like showed in table 5, HOMA-IR values were significantly higher in subjects with cardiometabolic abnormalities. It corroborates the idea that insulin resistance, although it is not the only, is considered to be an important contributor to cardiometabolic risk. Recent studies show that obesity, central obesity, high insulin response and insulin resistance, all independently and partially, contribute to cardiometabolic risk (29). The glycemic control, assessed by HbA_{1c}, has no correlation with the presence of cardiometabolic risk in this population but, certainly, its control constitutes the basis of treatment of these patients, aiming at the prevention of diabetes and cardiovascular diseases (30).

Intercorrelation of variables introduces collinearity into predictive statistical models, producing unreliable estimates and making it difficult to ascertain which variables represent the dominant physiological processes (31). Factor analysis has long been used in psychometric research to deal with this problem and has been an increasing use to analyze physiological relationships (10). In our results, factor analysis does not imply that insulin resistance causes dyslipidemia; rather, it demonstrates that these two phenotypes are very closely associated and defines a unique physiological domain.

In summary, factor analyses identify two independent factors underlying clustering of the basic cardiometabolic risk variables. A hyperglycemia and dyslipidemia define two distinct physiological domains linked together through mutual associations with fasting glucose levels. In our patients, insulin resistance plays an important role in the prevalence of cardiometabolic risk variables and the higher prevalence of atherogenic dyslipidemia makes necessary the adoption of measures for prevention of cardiovascular diseases.

Some limitations are present in our study: the first is that HOMA-IR is not the gold standard in the evaluation of insulin resistance. Nevertheless, this index correlates moderately well with insulin resistance as measured by hyperinsulinemic euglycemic clamp, which is considered to be the gold standard in the evaluation of insulin resistance (32). Thus, several large population studies have shown that the application of HOMA-IR is a good method for assessing insulin resistance across a range of glucose tolerance from normal to diabetes (33). A second limitation is that the study sample consisted primarily of white Brazilians, and the ability of the same metabolic markers or cut-points to predict poor glycemic control in overweight individuals of other ethnicities is yet to be proven.

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