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RESEARCH ARTICLE

ANTHROPOMETRIC AND BIOCHEMICAL MARKERS OF INSULIN RESISTANCE ACCORDING TO ADIPOSE TISSUE IN OVERWEIGHT AND OBESE PATIENTS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: The need to diagnose insulin resistance (IR) is increasingly relevant since an early diagnosis may lead to timely interventions that may slow down onset of associated diseases. Currently, the gold standard for assessing insulin sensitivity is the euglycemic clamp, however, its reproducibility at the clinical level is challenging. Hence, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and the oral glucose tolerance test (OGTT) are being used in the clinical setting to identify insulin resistance, prediabetes, and diabetes. Thus, the purpose of this study was to compare HOMA-IR with insulin curves and their association with early insulin resistance in overweight patients in relation to biochemical markers and anthropometric measurements. ***Methods***: This was descriptive cross-sectional study in 199 patients between 18 and 80 years of age for which demographic data, anthropometric measurements including body composition by bioelectrical impedance, and paraclinical tests (blood glucose, insulin, lipid profile) were performed. Measures of central tendency (mean or median) and dispersion (standard deviation or percentiles) were analyzed for quantitative variables according to data distribution. Shapiro-Wilk and Shapiro-Francia tests were performed to determine normality, which showed that none of the variables are normally distributed, and were therefore corrected with the Spearman correlation coefficient (non parametrical test). ***Results***: Correlation analyses between anthropometric and biochemical measurements (body mass index, hip perimeter, waist-to-hip ratio, waist-to-height ratio, glucose curves 0-120 min, and insulin curve 0-30 min) and body composition (body fat percentage, visceral adipose tissue, and HOMA-IR) were performed. This analysis showed a statistically significant association between insulin curve at 0-30 minutes and body fat percentage (rho= 0.3256; $p < 0.001$); (rho= 0.2383; p= 0.0007); visceral adipose tissue (rho= 0.2900; $p < 0.001$) and HOMA-IR (rho= 0.9835; $p < 0.001$); (rho= 0.5301; $p < 0.001$). No statistically significant association was identified between plasma glucose at 0 and 120 minutes and body fat percentage ($p< 0.1226$) or visceral fat ($p < 0.2471$). ***Conclusion***: By approaching the correlation between basal insulin at 0 and 30 minutes post-loading with VAT, BFP, and other anthropometric indices, we obtained results that strongly suggest that HOMA-IR and glucose curves are altered late and without correlation to the amount of adipose tissue.

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INTRODUCTION

Insulin resistance has been recently proposed to be the triggering factor for alterations that lead to diseases associated with adiposopathy. Insulin resistance (IR) can be defined as the reduced ability of the body to respond to insulin, whether it's due to deficient insulin production or use. During the initial stages, IR leads to compensatory over-production of insulin (hyperinsulinemia), which is easily observed during carbohydrate intake (Galgani *et al.,* 2012). As a consequence of hyperinsulinemia, hepatic lipogenesis is stimulated, plausibly favoring local processes such as steatosis (Trauner *et al.,* 2010). Similarly, decreased lipolysis favors an increase in circulating free fatty acids, especially low-density, favoring a state associated with dyslipidemia (Smith, 2007). Insulin resistance also affects glucose metabolism since hepatic glycogen storage is decreased, evidenced by an initial increase in basal plasma glucose levels followed by an increase in postprandial plasma glucose levels (Large *et al.,* 2004). Finally, the hypertensive effects of insulin have been well established, among which are its antinatriuretic effect, the effect on vascular smooth muscle cells, and endothelium, among others, which together with a state of insulin resistance favor sodium retention (Hu *et al.,* 1993), and thickening of the tunica intima and tunica media layers (Ridray, 1995), increased release of endothelin, thus favoring development of arterial hypertension (Stepniakowski

et al., 1995). The need to diagnose IR has become increasingly relevant since an early diagnosis may lead to establishment of early interventions that slow down onset of associated diseases (Ridray *et al.,* 1995; Bray *et al.,* 2018). Currently, the gold standard for assessing insulin sensitivity is the euglycemic clamp, however, its reproducibility at the clinical level is challenging. Therefore, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and the oral glucose tolerance test (OGTT) are the tools used in the clinical setting to measure insulin resistance in the context of prediabetes and diabetes, respectively (Consensus, 2019; Qu *et al.,* 2011). Nonetheless, there are currently gray areas in the interpretation and application of HOMA-IR and OGTT in different populations. Specifically, the HOMA-IR requires having increased basal glucose or insulin levels in order to achieve ranges of certain alterations, making this tool to be late in detection of the triggering event. Thus, the purpose of this study was to compare HOMA-IR with insulin curves and their association with early insulin resistance in overweight patients by analyzing biochemical markers and anthropometric measurements.

MATERIALS AND METHODS

This was descriptive cross-sectional study in patients attending the Obesity, Dysmetabolism, and Sports Center (COD^2) at Las Americas Clinic in Medellin, Colombia, during the first trimester of 2018. Patients attending the center for the first time, that were between 18 and 80 years of age, and willing to participate were included in this study. Patients with previous diagnosis of chronic disease, or were taking any kind of oral antidiabetic therapy, metformin, or corticoids were excluded from this study. The Ethics Committee at Las Americas Clinic approved this study. Demographic data, anthropometric measurements, and paraclinical examinations were taken during the first visit. Anthropometric measurements included body composition, body fat percentage (BFP), visceral adipose tissue (VAT), and waist, neck, and hip circumferences. A BFP > 33% in females, and >25% in males was considered as high; and an increased VAT was considered > 100 cm^2 (Ling *et al.,* 2011). Body composition measurements were performed using InBody 770® bioelectrical impedance analyzer (Lim *et al.,* 2009; Utter *et al.,* 2010). The following anthropometric indices that associate central adiposity and cardiovascular risk (Moreira Andrés, 2010) were included: waist-to-height ratio (WHtR) (Schneider *et al.,* 2010) -calculated by dividing the waist perimeter (cm) by the height (cm)-, and waist-to-hip ratio (WHR), calculated by dividing the waist perimeter (cm) by the hip perimeter (cm) (Medina-Inojosa *et al.,* 2018). Body mass index (BMI), was calculated by the Adolph Quetelet formula by dividing the weight in kilograms by the square of the height in meters (m^2) (Romero-Corral *et al.,* 2008), classifying patients as at risk of malnutrition (BMI < 18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI of 25-29,9 kg/m^2), obese (BMI>30 kg/m^2), and morbidly or extremely obese (BMI> 40 kg/m^2) (WHO, 2004). Samples for biochemical analysis were taken on site. Lipid blood tests (total cholesterol, HDL cholesterol, LDL, cholesterol, and triglycerides) were performed using enzymatic assays. International guidelines were followed to evaluate alterations in carbohydrate metabolism. Briefly, participants ingested a solution containing 75 gr of glycerol in 300 ml of water (American Diabetes Association, 2018). Based on the physiological model proposed by Ferrannini *et al.* and the Reaven study (Reaven, 1993; Matthews *et al.,* 1985) we evaluated basal insulin excursion and 30-min post-glycerol load. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was applied to all participants. This is an easy to use tool frequently used in population studies (HOMA-IR = fasting plasma glucose (mg/dL) x basal insulin (uU/mL)/405) (10,22). Based on previous studies (Bonora *et al.,* 1998; Acosta *et al.,* 2002; Giovana Solano, 2018), we defined insulin resistance as a HOMA-IR ≥ 3.0 in our study population. Anthropometric measurements included BMI, calculated by dividing the weight in kilograms (kg) by the square of the height in meters (m^2) (Romero-Corral *et al.,* 2008; WHO Expert Consultation, 2004). Waist-to-height ratio (WHtR) calculated by dividing the waist perimeter (cm) by the height (cm) was used as the measure with the greatest association to cardiovascular risk (Schneider *et al.,* 2010). Using a cutoff value of 0.5, WHtR is a good anthropometric index to determine central adiposity and to identify those individuals at greater cardio metabolic risk. Its usefulness lies in the fact that it can be used in different ethnicities and genders, and is given as a universal limit (Browning *et al.,* 2010). Similarly, the WHR ratio together with the WHtR show a direct correlation for prediction of mortality risk in obese and normal-weight adults, in addition to predicting metabolic syndrome and therefore insulin resistance (Reis *et al.,* 2009). Measures of central tendency (mean or median) and dispersion (standard deviation or percentiles) were analyzed for quantitative variables according to data distribution. Shapiro-Wilk and Shapiro-Francia tests were performed to determine normality, which showed that none of the variables are normally distributed, and were therefore corrected with the Spearman correlation coefficient (non parametrical test). A p-value < 0.05 was considered statistically significant. Data analysis was performed using STAT 14 software.

RESULTS

A total of 199 patients participated in this study. The majority of the participants were female (82.4%), and ages ranged between a minimum of 18 years and a maximum of 80 years, with a mean of 41 years of age, mode of 39 years, and standard deviation of 13.3 years. Regarding body composition, mean BMI was 28.67 Kg/m^2 (SD 4.7), mean BFP of 40.2% (SD 7.7), and mean and mode of VAT of 151.7cm^2 (SD 47.5) and 146 cm^2, respectively. Mean waist-to-hip ratio was 0.92 (SD 0.06), and mean waist-to-height ratio was 0.58 (SD 0.07). Mean insulin concentration measured at 0 and 30 minutes was 11.2uUI/mL (SD 6.5) and 90.5 uUI/mL (SD 65.9) respectively. In addition, mean glucose levels at 0 and 30 minutes was 91.4mg/dL (SD 10.7) and 103.8 mg/dL (35.05) respectively, with mean HOMA-IR values of 2.59 (SD 1.63), median of 2.27, and mode of 3.35. Characteristics of participating individuals are shown in Table 1. Shapiro-Wilk and Shapiro-Francia tests showed that none of the variables were normally distributed, and were therefore corrected with the Spearman correlation coefficient and the Kruskal Wallis test. BFP and VAT were analyzed as independent variables, and among the analyses with the lipid panel variables, a statistically significant association between BFP and VAT was found with HDL cholesterol ($p<0.001$), shown in tables 2 and 3, respectively. Correlation analysis between anthropometric and biochemical measurements (BMI, hip perimeter, WHR, and WHtR, glucose curves 0-120 min, and insulin curve 0-30 min) and body composition (BFP, VAT, and HOMA-IR) were performed.

Table1. Characteristics of study participants

Variable	n	%	Mean (SD)	Median	Interval
Age			43.14 (±13.3)	41	18 – 80
Gender	199				
- Male	35	17.6			
- Female	164	82.4			
Weight (Kg)			76.5 (±14.5)	73.5	45.4 – 122.3
Height (cm)			162 (±8.0)	162	146 – 187
BMI			28.6 (±4.7)	28.3	19.9 – 48
BFP (%)			40.2 (±7.7)	40.7	17.9 – 54.1
VAT(cm^2)			151.7 (±47.5)	150.7	41.6 – 247
Insulin 0min (uUI/mL)			11.2 (±6.50)	10.7	2.7 – 52
Insulin 30min (uUI/mL)			90.5 (±65.9)	75.9	3.36 – 426
Glucose 0min (mg/dL)			91.4 (±10.7)	90	69 – 163
Glucose 120min (mg/dL)			103.8 (±35.0)	97	42 – 297
HOMA-IR			2.59 (±1.63)	2.27	0.61 - 13

Table 2. Body fat percentage and lipid profile

Body Fat Percentage					
Variable	**Male**		**Female**		**p-value**
	BFP > 25% 31 (15.6%)	**BFP ≤ 25%** 4 (2.0%)	**BFP> 33%** 151 (75.8%)	**BFP ≤ 33%** 13 (6.5%)	
Total cholesterol	185 (152-212)	207 (189 – 235)	188 (162-219)	175 (166-232)	0.4402
HDL cholesterol	41.3 (38 - 46)	38.5 (35.5 - 47.5)	50 (43 - 58)	54 (42 - 64)	*0.0001*
LDL cholesterol	109 (90-138)	141 (114 -174)	115 (94-142)	97 (88 - 139)	0.3896
Triglycerides	127 (83-178)	108 (59-198)	117 (78-162)	116 (78-151)	0.7830
Tg/HDL ratio	1 (0.6 – 1.2)	0.6 (0.3 – 1.2)	0.8 (0.6 – 1.2)	0.8 (0.7 – 1.2)	0.4021

Table 3. Visceral Adipose Tissueand lipid profile

Visceral Adipose Tissue (VAT)					
Variable	**Male**	**Male**	**Female**	**Female**	**p-value**
	VAT> 100cm^2 28 (14.1%)	**VAT≤ 100 cm^2** 7 (3.5%)	**VAT> 100 cm^2** 141 (70.9%)	**VAT≤ 100 cm^2** 23 (11.6%)	
Total cholesterol	180 (149 - 211)	198 (186 – 226)	191 (164 - 219)	173 (156-230)	0.2306
HDL cholesterol	42.2 (37.5 -45.4)	40 (37 - 54)	50 (43 – 58)	51.6 (42.2 - 57.5)	*0.0001*
LDL cholesterol	108 (88 - 138)	125 (103.6 -157.2)	117 (95 - 142)	97 (74.8 - 139)	0.2067
Triglycerides	125 (83 - 184)	129 (86 - 172)	117 (78- 162)	112 (78 - 151)	0.8519
Tg/HDL ratio	1 (0.7 – 1.2)	0.7 (0.4 – 1.1)	0.8 (0.6 – 1.2)	0.9 (0.6 – 1.2)	0.5254

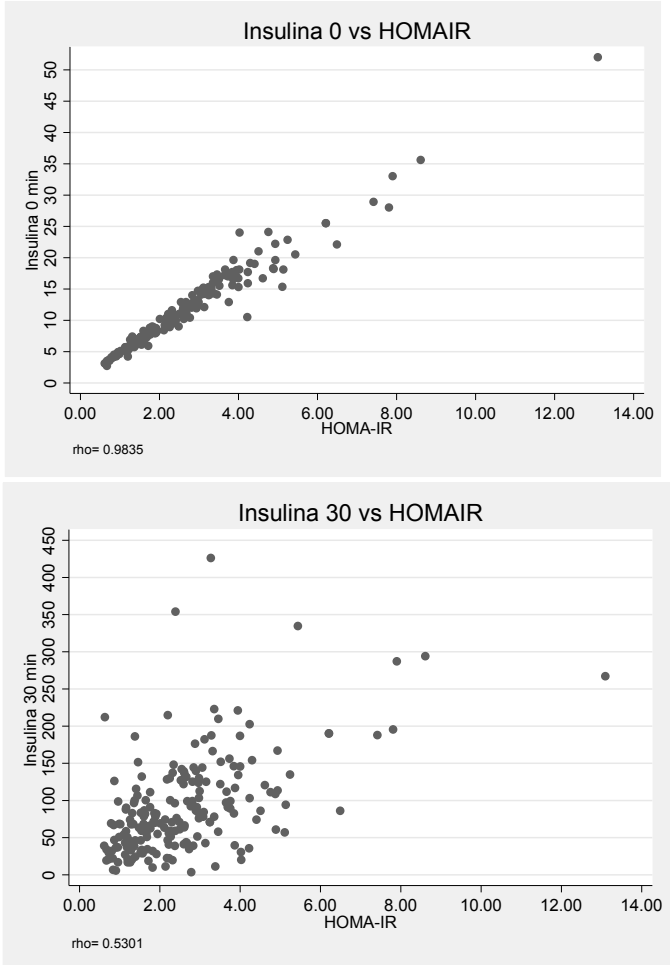
Table 4. Correlation analysis between anthropometric and biochemical measurements and body composition

Variable	**HOMA- IR**		**BFP**		**VAT**	
	rho	**p**	**rho**	**p**	**rho**	**p**
BMI	0.6070	<0.001	0.6596	<0.001	0.8177	<0.001
Waist-to-hip ratio (WHR)	0.3675	<0.001	0.4149	<0.001	0.6788	<0.001
Waist-to-height ratio (WHtR)	0.4981	<0.001	0.3256	<0.001	0.4479	<0.001
Insulin 0 minutes (uUI/mL)	0.9835	<0.001	0.3256	<0.001	0.4479	<0.001
Insulin 30 minutes (uUI/mL)	0.5301	<0.001	0.2383	0.0007	0.2900	<0.001
Glucose 0 minutes (mg/dL)	0.4602	<0.001	*0.1098*	*0.1226*	*0.2471*	*0.0004*
Glucose 120 minutes (mg/dL)	0.3725	<0.001	*0.1560*	*0.0278*	*0.2231*	*0.0015*
BFP	0.3267	<0.001	-	-	-	-
VAT	0.4649	<0.001	-	-	-	-

Table 5. Multivariate analysis

	Bivariate		**Multivariate**	
Variable	**Coefficient (CI 95%)**	**p-value**	**Coefficient (CI 95%)**	**p-value**
WHR	10.9 (7.7 ; 14.2)	<0.001	0.3 (-0.9 ; 1.7)	0.607
WHtR	9.1 (6.4 ; 11.9)	<0.001	0.4 (-0.8 ; 1.6)	0.565
INSULIN 0 min	0.25 (0.24 ; 0.25)	<0.001	0.24 (0.22 ; 0.24)	<0.001
INSULIN 30 min	0.01 (0.01 ; 0.02)	<0.001	0.0001 (-0.001 ; 0.001)	0.771
BFP	0.05 (0.02 ; 0.1)	0.001	-0.022 (-0.039 ; -0.045)	0.014
VAT	0.02 (0.01 ; 0.03)	<0.001	-0.003 (-0.001 ; 0.0068)	0.737

This analysis showed a statistically significant association between insulin curve at 0-30 minutes and BFP (rho= 0.3256; $p < 0.001$); (rho= 0.2383; p= 0.0007); VAT(rho= 0.2900; $p < 0.001$) and HOMA-IR (rho= 0.9835; $p < 0.001$); (rho= 0.5301; $p < 0.001$) (table 4 and Figure 1). No statistically significant association was identified between plasma glucose at 0 and 120 minutes and BFP ($p<0.1226$) or VAT ($p < 0.2471$). Bivariate linear regression analysis using HOMA-IR as an independent variable, the coefficient for WHR showed that for each increased percentage unit, the HOMA-IR index is expected to rise on average 10.9, suggesting this could be a possible early factor of insulin resistance. In addition, our we found that the basal insulin coefficient (bivariate) showed that for each increase in uUI/mL, the HOMA-IR index is expected to rise on average 0.25. On the other hand, in the multivariate analysis only basal insulin and BFP were statistically significant (Table 5).



Scatter plots(A)shows the very significant correlationbetween basal insulin and HOMA-IR, and scatter plots(B), shows high scatter between the variables insulin 30 min and HOMA-IR,

Figure 1. Relationship between basal insulin (A) and insulin 30 minutes after loading (B) and HOMA-IR

DISCUSSION

The purpose of this study was to compare HOMA-IR with insulin curves and their association with early insulin resistance in overweight patients by analyzing biochemical markers and anthropometric measurements. Among the anthropometric measurements, our study showed that WHR and WHtR exhibited a moderate positive correlation with BFP, VAT, and HOMA-IR. Keeping in mind that the average BMI in our study population was 28kg/m^2, BMI similarly showed a strong positive correlation with VF, suggesting that degrees of overweight may already require mandatory medical interventions aiming at reducing inflammation and associated co morbidities. It is worth to point out that although efforts were made to have a single professional perform all anthropometric measurements, due to availability issues a different professional performed some of the measurements, which may have generated measurement bias. Regarding biochemical markers, our study showed that the insulin curve exhibited a moderate positive association with VAT, and mildly positive association with BFP, being the basal insulin correlation more striking. This may be partly explained by the previously described association of VAT and inflammation with generation of insulin resistance. The very strong positive correlation between basal insulin and HOMA-IR, with mean of 11.2(±6.50) uUI/mL, suggests that this may be the most relevant aspect of the HOMA-IR equation, even more so than the moderate positive correlation of basal plasma glucose, which, together with anthropometric indices, may be considered as a crucial test for patient evaluation. Interestingly, our analyses showed a low, non-statistically significant correlation between glucose curve and BFP and VF. Likewise, lipid profile was not significantly associated with BFP and VAT, except HDL cholesterol, whose low levels were significantly associated with BFP as well as with VAT. The relevance of these findings lies in the fact that in multiple studies as well as in the clinical practice, these paraclinical tests are frequently requested for metabolic evaluation, however they are not strongly associated to body composition, likely because they are late manifestations of high content of body fat. Thus, alterations in these tests may relate to chronicity of the high fat content that leads to damage of the balance between organs, as postulated in the *CLARO's theoretical model* that suggests that organokine dysfunction precedes fatty acid and glucose alterations, among others (Rosero *et al.,* 2018). Finally, while our study was not aimed at determining normal HOMA-IR values in our population, it is worth to point out that mean HOMA-IR values were comparable to those reported by studies in non-Latino populations, and considering that our sample was comprised by individuals with high contents body and visceral fat, the HOMA-IR showed a moderate positive correlation with BFP and VAT, which in turn implies that the observed increase in HOMA-IR values to ranges of insulin resistance depends on the chronicity of this relationship, however our sample size may limit the reliability of predicting a true mean cutoff point. In addition, the predominance of female subjects may subject our results to selection bias. Future studies should include larger samples and provide an approximate cutoff point for HOMA-IR values in a homogeneous and universal population. Our results are in agreement with those reported by Bray and colleagues (8), in which the pathologic increase in adipose tissue is proposed as a key determinant in the genesis of non-transmissible chronic diseases. In addition, in the current and constant search for an optimal marker for early diagnosis of adiposopathy, due to the promising results, specific markers of adipose tissue such as adiponectin have been postulated as such. However, these tests are costly and challenging to implement in the clinical setting. Therefore, the relevance of the results presented herein lies in the ability to show that anthropometric measurements (WHR and WHtR) together with the insulin curve (0-30 min) are valuable tools presenting a suitable correlation and ease of use, highly replicable, and of low cost in our setting, allowing clinicians to perform an evaluation guided towards determining when adipose tissue is generating alterations that may ultimately lead to insulin resistance.

Conclusion

The search for early markers of adiposopathy and insulin resistance is a currently a subject of great scientific interest. In this study, by approaching the correlation between basal insulin at 0 and 30 minutes post-loading with VAT, BFP, and other anthropometric indices, we obtained results that strongly suggest that HOMA-IR and glucose curves are altered late and without correlation to the amount of adipose tissue. However, when analyzing insulin at 0 and 30 minutes post-loading a moderate correlation with BFP and VAT can be observed, independently of BMI, which could be considered as an early marker of adiposopathy that may lead to insulin resistance. This is subjected to the size and type of sample included in our

study, which could be considered as a limitation in our study. Therefore, identifying simple, more economical, and replicable methods of analysis such as insulin levels and body composition- makes this study of great value as it can be easily implemented in the clinical setting. Furthermore, our study highlights that in order to provide better care for our patients, the focus should be on finding timely, accessible, and adequate markers that can be used in large populations.

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