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ORIGINAL ARTICLE

Relationship between insulin-biochemical resistance levels and the degree of depression and anxiety in patients from Honduras

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Abstract

Background/purpose Many studies suggest that insulin resistance in obese patients bridges mental illness. Our objective was to identify the association between levels of depression and anxiety with insulin resistance, and its relationship with obesity and abdominal obesity

Methods A cross-sectional analytical study was carried out in Honduras. Sociodemographic variables, anthropometric parameters, HOMA index, and level of severity of anxiety and depression were collected, and a descriptive, bivariate, and multivariate were performed.

Results In a sample of 381 adult patients, the bivariate analysis showed a statistic association of insulin resistance with all remaining variables. However, multivariate analysis showed a significative association of anxiety with BMI, depression, waist circumference, and insulinemia, while depression was associated with HOMA, anxiety, insulinemia, glycemia, and waist circumference.

Conclusions Our results provide important evidence of a direct and growing association between HOMA-IR and the severity of depression, and indirectly with anxiety. Secondarily, also with anthropometric factors (BMI and WC), traditionally associated with cardiovascular risk. This finding has important implications both for the early diagnosis of these mental pathologies, taking into account HOMA-IR values, and for preventive interventions focused on maintaining blood insulin levels.

Keywords Depression · Anxiety · Insulin Resistance · Obesity

Introduction

In the past few years, there has been an interest in studying the possible association between biochemical insulin resistance (IR), developed in the context of abdominal obesity, and the clinical manifestations of psychiatric diseases such as anxiety and depression. There is scientific evidence showing insulin resistance as the main pathophysiological substrate of these mental disorders [1, 2]. In the connection among all these factors, it is worth wondering which disorder is the source and support of the others.

In general, nearly 13% of the world's adult population is obese [3]. In case of the capital city of Honduras, Tegucigalpa, the prevalence values of obesity in women and men aged

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between 20 and 64 years are 27% and 18%, respectively [4]. On the other hand, in this same population, the prevalence of the depressive syndrome reaches 26.4%, whereas that of anxiety is 5.7%. Curiously, it has been observed that excess weight and morbid abdominal circumference are frequently concomitant with these affective disorders in a large part of this population [5, 6].

Obesity is associated with an excessive accumulation of abdominal fat and to insulin resistance [7]. The metabolic changes linked to obesity seem to exert a negative repercussion on the psychological sphere [8]. Consequently, in a number of studies, it has been observed that obesity is a predictor of long-term depression [9] or also the coexistence of abdominal obesity with anxiety and depression [10]. In addition, it seems that factors such as the accumulation of perivisceral fat and the distribution of body fat are related with higher anxiety and depression scores in both genders [11]. Even so, there is controversy regarding this issue, since some studies have suggested a weak or null association between metabolic syndrome and anxiety or depression [12].

Many studies suggest that the absence or reduction of sensitivity to insulin in obese patients establishes a connection with mental ailments. Therefore, a number of studies illustrate this bidirectional relationship showing that the depression and anxiety symptoms are positively correlated with the fasting plasma insulin concentrations, and inversely correlated with sensitivity to insulin [13]. Additionally, this alteration produces adaptive metabolic changes positively correlated with the clinical manifestations of depression [14].

At the brain level, a number of experimental studies have confirmed the neuroprotective function of insulin, ensuring synaptic plasticity. However, the insulin receptor dysfunction leads to an increase in dopamine degradation, which can be the basis for the depressive symptoms [2]. Furthermore, mechanisms have been proposed in which inadequate insulin signaling modifies the neurogenesis of the hippocampus, synaptic plasticity, the response of the hypothalamic-pituitary-adrenal (HPA) axis, and the reward system, which would favor the onset of depressive states [15].

Factors associated with geography, such as the number of sunlight hours, the urban organization [16] or even psychosocial factors inherent to each culture [17] might exert a direct or indirect influence on the relationship between biological factors (biochemical or anthropometric) and this type of mental health problems. Given the above, and due to the still limited availability of information related to different environments, this study was designed with the objective of identifying the association of depression and anxiety with IR, and of determining how the degree of these pathologies influences such association. In addition, it intends to elucidate the relationship between this association and obesity. All of the above will allow proposing a new approach on treatment lines that may assist in the therapeutic management of these patients.

Material and methods

Design

A cross-sectional study was carried out.

Study population

Adult patients presenting anxiety and/or depression symptoms and signs, who attended the Dr. Mario Mendoza Acute Psychiatric Hospital between February 2018 and August 2020, referred from Primary Health Care centers across the entire country were included.

The exclusion criteria were (i) pregnancy; (ii) complicated chronic disease; (iii) use in the last 6 months of antidepressants, anxiolytics, anticolinergics, antihistamines, antiarrhythmics, antihypertensives, digitalis drugs, beta-blockers, thiazide diuretics, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, glucocorticosteroids/anabolics, or oral contraceptives; (iv) smoking habit and/or alcoholism; and (v) drug use or abstinence (cocaine and amphetamines).

Data collection

The data collection was carried out in a two-step procedure: (i) in the medical consultation the specific variables of the study (anthropometric variables, anxiety and depression) were taken together with the identification data of the patient and analytical tests for biochemical variables were requested. (ii) Subsequently, through the hospital's electronic registry, the results of biochemical variables and sociodemographic data of the patients were obtained.

Anthropometric measures

The body mass index (BMI) was calculated, in kg/m^2.Abdominal obesity was determined with an anatomical tape by measuring the waist circumference (WC) and categorized as follow: (i) in men: 94–101 cm, increased cardiovascular risk (ICR); ≥ 102cm, high cardiovascular risk (HCR); (ii) in women: 80–87 cm, ICR; ≥ 88 cm, HCR.

Determination of biochemical insulin resistance

The HOMA index was measured to determine insulin resistance considering the following equation:

$$\text{HOMA} = \frac{f\text{asting glycaemia } \left(\frac{\text{mg}}{\text{dl}}\right) \text{ x insulinemia} \left(\frac{\mu\text{Ui}}{\text{ml}}\right)}{405}$$

Indicating insulin resistance with HOMA index values ≥ 3.2 [18].

Determination of the depression and anxiety severity levels

The Hamilton scales for anxiety and depression were used. The Hamilton scale for depression is a 17-item questionnaire. Its total score varies from 0 to 52. The following cutoff points are suggested: not depressed: 0–7 mild/minor depression: 8–13 moderate depression: 14–18 severe depression: 19–22 very severe depression: >23 [19]. The *Hamilton* anxiety rating scale-HARS has 14 items with a total score ranged from 0 to 56 points and classified as follows: 0–5 points: no anxiety, 6–14 points: mild anxiety, >15 points: moderate/severe anxiety [20].

Data analysis

The IBM SPSS Statistics v25 program was used. A descriptive analysis of the qualitative variables through of absolute and percentage frequencies, and quantitative variables by means of central tendency, dispersion, and position measures was performed. It was assessed if IR (as a dichotomous variable) was statistically associated with the outcome variables (anxiety and depression), as well as with other independent variables (sociodemographic and clinical). For qualitative variables, the inference was performed through Pearson's Chi-square test or Fisher's exact test and the effect size was measured through odds ratios (OR). For the quantitative variables, the comparison of means test was performed, and the effect size was measured with Cohen's *d*. A correlation matrix between quantitative variables was also constructed. Finally, multivariate regression models were constructed to avoid confusion biases resulting from the non-randomization of the sample. In these models, adjusted ORs of each variable and the significance of the models themselves were obtained. In all the aforementioned analyses, significance was established with *p*-values below 0.05.

The calculation of the sample size for the comparison of proportions or means requires previous information that we lack because this is the first study carried out in our area with this objective. Therefore, it is an exploratory analysis; however, the Gpower software was used to calculate the post hoc power (1-beta) of the analyses by introducing the sample size obtained, a significance of 0.05 and the observed effect size, accepting only results higher than 0.8 which is the standard value commonly defines an analysis with sufficient statistical power.

Ethical criteria

Before the study was initiated, its protocol was approved by the Medical Ethics Committee (CR-061) of the Dr. Mario Mendoza Acute Psychiatric Hospital in Tegucigalpa. Once informed about the study dynamics and objective, the participants voluntarily signed an informed consent before their inclusion. The study was conducted according to the recommendations set forth in the Declaration of Helsinki for biomedical research studies in human beings. No invasive tests or samplings were required besides those derived from the routine care practice, and the information was duly coded to anonymize the clinical data prior to their tabulation and analysis.

Results

A sample consisting of 381 adult patients aged between 24 and 59 years was obtained, with a mean/standard deviation of 43±11.2 years, and with majority of females (74%).

According to the HOMA index, an IR rate of 81.1% was observed in 309 patients, who were distributed into the following degrees: 6 (1.9%), mild; 140 (45.3%), moderate; 137 (44.3%), high; and 26 (8.4%), severe.

Table 1 assesses the statistical association between IR and other qualitative variables. A statistical association was observed with all the variables (gender, BMI, waist circumference, and the "anxiety" and "depression" outcome variables). ORs of the ordinal categories presented a growing trend in each case, reflecting an increasingly higher risk at each step up in the levels.

Table 2 shows a statistical association analysis similar, but with numerical variables, observing such type of association in all the variables, except for age. Nevertheless, Cohen's *d*, which considers an important effect with values above 0.8, was obtained only for the insulinemia values and the scores obtained in the Hamilton scales.

The correlation matrix (Table 3) showed that most of the variables were significantly correlated, but with irrelevant correlation coefficients. The best correlation coefficients were obtained for the HOMA-insulinemia, BMI-weight, and Hamilton's anxiety-depression score pairs. These two scores obtained correlations coefficients similar to HOMA, whose value reached 0.5, indicating a moderate correlation.

Finally, for each outcome (depression and anxiety), two types of multivariate models were conducted: logistic (upper part of Table 4) and linear (lower part of Table 4).

The models for anxiety showed that the scores obtained in the depression scale and in insulinemia were significant. Furthermore, the logistic regression model also showed statistical significance for BMI and waist circumference. Similarly, in the models for depression, insulinemia, HOMA, and the scores of anxiety scale were significant; additionally, each model showed the statistical association with other variables. Some variables were not significant, but were kept as part of the model because, when they were removed, the quality of the model was reduced.

The quality of the logistic regression models has been expressed through the Akaike information criterion (AIC),

Table 1 Association of insulin resistance with qualitative variables

Variables	Total *n* (%)	IR *n* (%)	No IR *n* (%)	*p*-value	OR (CI95%)
Sex (% females)	281 (73.1)	236 (76.4)	45 (62.5)	0.016	1.92 (1.08–3.44)
BMI				<0.001	
Healthy weight	57 (14.9)	48 (15.5)	9 (12.5)		ref
Overweight	179 (46.9)	125 (40.5)	54 (75.0)		0.43 (0.20–0.95)
Obesity I	87 (22.8)	79 (25.6)	8 (11.1)		1.85 (0.67–5.12)
Obesity II	58(15.2)	57 (18.4)	1 (1.4)		10.69 (1.31–87.40)
Waist circumference (risk)	233 (61.2)	212 (68.6)	21 (29.2)	<0.001	5.29 (2.93–9.79)
Anxiety (yes)	314 (82.4)	273 (88.3)	41 (56.9)	<0.001	5.55 (3.03–11.11)
Anxiety categories				<0.001	
Not anxiety	67 (17.6)	36 (11.7)	31 (43.1)		ref
Mild	136 (35.7)	98 (31.7)	38 (52.8)		2.22 (1.21–4.08)
Moderate/severe	178 (46.7)	175 (56.6)	3 (4.2)		50.23 (14.56–173.27)
Depression (yes)	296 (77.7)	264 (85.4)	32 (44.4)	<0.001	7.14 (4.00–14.29)
Depression categories				<0.001	
Not depressed	85 (22.3)	45 (14.6)	40 (55.6)		ref
Mild	101 (26.5)	76 (24.6)	25 (34.7)		3.42 (1.84–6.36)
Moderate	71 (18.6)	64 (20.7)	7 (9.7)		10.3 (4.23–25.02)
Severe	35 (9.2)	35 (11.3)	0 (0)		NA
Very severe	89 (23.4)	89 (28.8)	0 (0)		NA

IR, insulin resistance; *OR*, odds ratio; *ref*, reference category; *NA*, not available

and the quality of the linear models is shown through their statistical significance and both presented $p< 0.001$.

Discussion

Depression and anxiety are highly prevalent health problems in the world population, and seem to have a metabolic substrate related to IR [21–24].

We found an association of depression and anxiety with biochemical IR (HOMA) as qualitative (Table 1), as quantitative (Table 2) bivariate analyses. Furthermore, higher ORs for anxiety and depression were observed for IR group and these risks increased according to the severity of the pathologies. A correlation between these three variables was also observed. However, the multivariate models have shown an association between the HOMA-depression binomial on the one hand (adjusted OR=6.67) and the anxiety-depression binomial variables. The HOMA-anxiety association observed in the bivariate analysis has not been confirmed in the multivariate models, evidencing a confusion bias. Nevertheless, all analysis performed showed the statistical association between the HOMA and depression values, either considered as continuous or as categorical variables, also showing clinical relevant effect size. These results would imply that there is a hormone-related component, insulinemia, acting as a risk factor for depression and, indirectly, for anxiety due to the association between them [25]. Previous studies have confirmed a

Table 2 Association of insulin resistance with quantitative variables

Variables	Total Me [P_{25}-P_{75}]	IR $\bar{x}$ (SD)	No IR $\bar{x}$ (SD)	*p*-value	Cohen's d (CI95%)
Age (years)	43 [30–52]	41.60 (11.35)	41.42 (10.71)	0.445	0.02 (–0.24,0.27)
Waist circ. (cm)	96 [89–100]	97.99 (15.53)	90.81 (6.34)	<0.001	0.5 (0.25,0.76)
Glycaemia (mg/dl)	94 [90–99]	95.39 (14.05)	92.14 (6.52)	0.001	0.25 (–0.01,0.51)
BMI (kg/m^2)	28.57 [21.17–32.50]	30.29 (5.79)	27.78 (2.56)	<0.001	0.47 (0.21,0.73)
Insulinemia (μUI/mL)	17.03 [14.20–20 20]	19.16 (5.26)	13.01 (1.18)	<0.001	1.29 (1.03,1.55)
Anxiety score	14[8–23]	18.49 (10.89)	7.39 (3.94)	<0.001	1.11 (0.86,1.37)
Depression score	14 [8–22]	17.43 (9.76)	7.94 (3.94)	<0.001	1.06 (0.8,1.32)

Circ, circumference; *Me*, median; *P*, percentile; $\bar{x}$ mean; *SD*, standard deviation; *IR*, insulin resistance

Table 3 Correlation matrix

	Waist circ. (cm)	Age (years)	Glycaemia (mg/dl)	HOMA	BMI (Kg/m^2)	Insulinemia (μUI/mL)	Weight (kg)	Anxiety Score	Depression score
Waist circ. (cm)	Corr coef (*p*-value)	0.27 (<0.001)	0.19 (<0.001)	0.45 (<0.001)	0.52 (<0.001)	0.34 (<0.001)	0.55 (<0.001)	0.31 (<0.001)	0.26 (<0.001)
Age (years)			0.21 (<0.001)	0.11 (0.038)	0.09 (0.092)	0.02 (0.688)	0.03 (0.591)	0.13 (0.013)	0.16 (0.002)
Glycaemia (mg/dl)				0.19 (<0.001)	0.13 (0.009)	–0.18 (<0.001)	0.14 (0.005)	0.07 (0.165)	0.11 (0.038)
HOMA					0.33 (<0.001)	**0.85**	0.24 (<0.001)	**0.51**	**0.50**
BMI (kg/m^2)						0.22 (<0.001)	**0.84**	0.14 (0.005)	0.14 (0.008)
Insulinemia (μUI/mL)							0.15 (0.003)	0.42 (<0.001)	0.40 (<0.001)
Weight (kg)								0.04 (0.456)	0.05 (0.339)
Anxiety score									**0.84**
Depression score									

Significances of all bold entries are $p < 0.001$

Circ, circumference; *BMI*, body mass index; *corr coef*, correlation coefficient; *IR*, insulin resistance

Table 4 Multivariate regression models

Multivariate regression logistic models						
Independent variables	Anxiety model (AIC: 327.41)			Depression model (AIC: 259.73)		
	Coef	*p*	OR (CI95%)	Coef	*p*	OR (CI95%)
β_0	2.94	0.004	18.92 (2.64–147.78)	0.47	0.826	1.60 (0.02–125.99)
BMI	0.06	0.034	1.06 (1.01–1.13)			
Depression Sc	0.19	<0.001	1.20 (1.16–1.27)			
Waist circ (Risk incr)	0.87	0.01	2.39 (1.24–4.68)	0.84	0.021	2.33 (1.14–4.81)
Insulinemia	0.12	<0.001	1.12 (1.06–1.19)	0.37	0.003	1.45 (1.13–1.87)
Anxiety Sc				2.29	<0.001	1.33 (1.25–1.43)
Glycaemia				0.05	0.046	1.04 (0.99–1.10)
HOMA				1.91	0.002	6.67 (2.00–25.00)
Multivariate regression lineal models						
Independent variables	Anxiety model (model *p*-value: <0.001)			Depression model (model *p*-value: <0.001)		
	Coef	*p*	Adjusted *R* squared	Coef	*p*	Adjusted *R* squared
$\boldsymbol{\beta_0}$	1.38	0.492	0.625	–0.45	0.781	0.629
Weight	0.04	0.097				
Depression Sc	0.83	<0.001				
Insulinemia	0.29	<0.001		0.23	0.022	
HOMA				1.91	<0.001	
Anxiety Sc				0.64	<0.001	
Age				0.05	0.053	
Sex (male)				–1.32	0.061	

BMI, body mass index; *Sc*, score; *Waist circ*, waist circumference; *Risk incr*, risk increased; *Coef*, coefficient; *AIC*, Aikake information criterion; *OR*, odd ratio

positive relationship between IR and depression, although not with anxiety [14].

Obesity is one of the most important risk factors for health, and one of its main complications is insulin resistance [26]. This association, as is the case in other studies [27–28], has been verified in our results. Due to their relationship with obesity and cardiovascular diseases [29], BMI and abdominal waist circumference were evaluated finding statistical significance in the logistic regression models for both parameters; BMI, for the anxiety model, and WC, for both anxiety and for depression models. However, they were not significant in the linear models. This could be due to that the changes in the numerical values from the anxiety and depression tests associated with these independent variables were small, although sufficient for changing the subjects from healthy to illness categories. It means that the changes observed were numerically small, but clinically relevant. Thus, as previously described [5, 30], obesity, through BMI and WC, is associated with depression and anxiety, either due to endocrine-based physiological mechanisms or through psychosocial factors such as self-perception of body image or self-esteem, widely associated with obese individuals. A previous study showed that abdominal obesity was associated to major depressive disorder, but not with generalized anxiety, although it included adults younger than 22 years only [31].

Regarding gender, women in our study present almost twice the risk (OR=1.92) for IR. However, it is described that healthy women present higher sensitivity to insulin than men [32, 33]. This discrepancy can be related to the age distribution among women, since half of them were over 45 years old and 25% were between 52 and 59 years old. Therefore, they were close or already going through menopause, and there could be a loss of sensitivity to insulin and an increased abdominal adiposity related with estrogen deficit [34].

Nevertheless, in the multivariate models, the gender factor did not attain statistical significance either for depression or anxiety, with only a statistical trend being observed in the linear regression model for depression indicating that female gender is a risk factor for depression (Table 4). Statistical significance was probably not reached due to the sample size. However, when the gender variable was removed the model fit (adjusted R^2=0.63) worsened, thus confirming the influence of this variable. In fact, it has been described that depression is linked to gender, being more prevalent in women [35, 36] and showed a greater association between depression and IR in women than in men [24].

Regarding age, in the bivariate analysis little association was observed, finding the best statistical significance between age and depression, although with a negligible correlation coefficient. In the multivariate analysis, only the linear regression model for depression presents certain statistical trend of the effect of age, not attaining significance. In this sense, a number of studies corroborate higher prevalence of depression with age [31], although association between IR and depression in adolescents has also been reported [37, 38].

Even so, the effect of age or gender on the association between IR and depression/anxiety might also be explained by other factors such as poverty, violence, and gender and ethnic inequalities [35], an aspect not addressed in this research.

Our results have important clinical implications, since the biological factors studied can be adopted for the early diagnoses of these pathologies and they are also associated with cardiovascular diseases, which are the leading cause of death worldwide [39].

Both the cardiovascular problems and the risk factors associated with the depression and anxiety disorders are very frequent reasons for consultation appointments in primary care, reason why the correct counseling from primary care to maintain a healthy anthropometry and a good insulin sensitivity could significantly reduce the morbi-mortality of the general population at the physical, psychological and emotional levels.

Strengths and limitations

Cross-sectional studies present the limitations inherent to observational studies; however, they are cost-effective and useful to identify prevalence values and risk factors associated with health problems.

The main limitation is the non-randomization during the recruitment of patients, but this has been solved by multivariate analysis, preventing confusion bias derived from a single bivariate analysis, as is the case in previous studies [5]. Furthermore, previous studies have reported the statistical association between IR-HOMA and depression, but many of them did not report the effect size [21, 24], while others that did, obtained lower odd ratios [23].

Finally, the sample size might have been insufficient to attain significance in some variables; however, the study has enough statistical power to meet the objectives set forth. Thus, these limitations do not affect the internal validity of the study to meet the objectives set forth for the Honduran population.

Conclusion

These results provide important evidence of a direct and increasing association between HOMA-IR and the severity of depression and, indirectly, with anxiety. Therefore, insulin resistance is an important risk factor for the onset of these mental ailments. Secondarily, evidence is also shown of the association between anthropometric factors (BMI and WC), traditionally associated with cardiovascular risk, and the presence of these mental health problems.

This finding has important implications both for the early diagnosis of these mental pathologies, considering the HOMA-IR values, and for preventive interventions focused on maintaining the levels of blood insulin.

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Declarations

Ethics approval and consent to participate This was a research involving human participants. All participants were informed about objectives and dynamic of the study and all of them affirmed that they understood this information and signed the informed consent to participate in the study. The study protocol was previously reviewed and accepted by a competent ethics committee as indicated in the methods section.

Conflict of interest The authors declare no competing interests.

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