

Relationship Between Insulin Resistance and Monocyte Count by Nutritional Status

Relación entre resistencia a la insulina y recuento de monocitos por estado nutricional

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Summary

Objective: to analyze the relationship between insulin resistance and monocyte count by nutritional status. **Methods:** analytical cross-sectional study, carried out at the Family Medicine Unit No. 80 in Morelia, Michoacán. Forty-five adults of both genders aged 18-55 years were selected by non-probabilistic sampling. Anthropometry, blood collection for blood biometry, blood chemistry, and insulin receptor expression in monocytes were performed. Patients with chronic diseases and altered immunocompromised states were excluded. Six groups were studied according to body mass index category, and with/without insulin resistance (IR). Median, minimum-maximum value was used. For comparisons between groups, the Kruskal-Wallis test, and Dunn's multiple comparison test were used as post-hoc. Statistical significance was considered with $p < 0.05$. **Results:** in adults with normal weight ($n = 19$), 63% presented IR. There was no difference in the number of classical, intermediate, and non-classical monocytes in patients with insulin resistance ($p > 0.05$). No differences were identified in the expression of the insulin receptor in monocyte populations ($p > 0.05$). **Conclusion:** a high proportion of insulin resistance was found in individuals with normal weight. Future studies are proposed on the influence of insulin resistance on intracellular signaling and secretion of proinflammatory cytokines derived from different monocyte subtypes in individuals with and without IR.

Keywords: Obesity; Glucose; Monocytes; Insulin Resistance.

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Resumen

Objetivo: analizar la relación entre resistencia a la insulina y recuento de monocitos por estado nutricional. **Métodos:** estudio transversal analítico, realizado en la Unidad de Medicina Familiar No. 80 de Morelia, Michoacán. Mediante muestreo no probabilístico, se seleccionaron 45 adultos, de ambos sexos de 18-55 años. Se les realizó antropometría, recolección sanguínea para biometría hemática, química sanguínea y expresión de receptor de insulina en monocitos. Se excluyeron pacientes con enfermedades crónicas y estados de inmunocompromiso alterado. Se estudiaron seis grupos de acuerdo con la categoría de índice de masa corporal y con/sin resistencia a la insulina (RI). Se utilizó mediana, valor mínimo-máximo. Para las comparaciones entre grupos se utilizó la prueba de Kruskal-Wallis y prueba de comparación múltiple de Dunn como post-hoc. Se consideró una significancia estadística con $p < 0.05$. **Resultados:** en adultos con normopeso ($n = 19$), 63% presentó RI. No hubo diferencia en el número de monocitos clásicos, intermedios y no clásicos en pacientes con resistencia a la insulina ($p > 0.05$). No se identificaron diferencias en la expresión del receptor de insulina en las poblaciones monocitarias ($p > 0.05$). **Conclusión:** se encontró una elevada proporción de resistencia a la insulina en personas con normopeso. Se proponen estudios futuros sobre la influencia de resistencia a la insulina en la señalización intracelular y secreción de citocinas proinflamatorias derivados de diferentes subtipos de monocitos en personas con y sin RI.

Palabras clave: Obesidad, glucosa, monocitos, resistencia a la insulina.

Introduction

The World Health Organization defines obesity (OB) as the abnormal or excessive storage of fat, secondary to energetic, pharmacological, or genetic imbalances.¹ Its high prevalence and rapid spread have led it to be considered “the pandemic of the 21st century”.² Worldwide, it is estimated that more than 39% of people over 18 years of age are overweight (OW) and 13% have OB.³ In Mexico, the National Health and Nutrition Survey (ENSANUT) 2022 reported a prevalence of OW, and OB of 75.2% in people ≥ 20 years of age.^{4,5}

Adipose tissue (AT) is composed mainly of adipocytes, which are fundamental in energy storage and endocrine activity, as well as vascular stroma (fibroblasts, endothelial cells, smooth muscle) that facilitates the flow of oxygen to the tissue, and infiltration of immune cells (macrophages, eosinophils, T cells, among others).⁶ During progression to OB, this infiltrate in AT is modified, increasing the number of proinflammatory cells in the tissue, mainly M1 or “classically activated” macrophages, which derive from local proliferation in AT, and recruitment of monocytes attracted from the peripheral circulation by chemoattractant molecules.⁷ In OB, both adipocytes and AT-infiltrating immune cells alter their secretory profile from an anti-inflammatory cytokine profile to a low-grade proinflammatory profile.⁸ Chronic high caloric intake triggers compensatory physiological mechanisms to neutralize glycemic peaks, mainly by increasing pancreatic secretion of insulin, a hormone that promotes post-absorptive metabolism in the body, facilitating the entry of glucose and amino acids into insulin-dependent tissues, such as skeletal muscle, AT, and liver.⁹

Constant exposure to high levels of insulin decreases the ability of the insulin receptor to transduce signals, promoting systemic states of “insulin resistance” (IR).¹⁰ Clinically, the most commonly evaluated index to determine systemic IR is the HOMA-IR index.¹¹ Since glucose is the metabolic substrate of choice in the body, all somatic cells express insulin receptors, with a higher density of expression found in hepatocytes, adipocytes, and musculoskeletal fibers.⁹ The normal number of monocytes in the blood circulation ranges between 6% and 8% of total leukocytes, which upon migration to peripheral tissues differentiate into macrophages.¹² Three subpopulations of monocytes have been described: classical (CD14⁺⁺16⁻), intermediate (CD14⁺⁺16⁺), and non-classical (CD14⁺16⁺⁺), which perform different immunological functions.¹³ In OB, the circulating proportion of these monocytes may be affected, with higher total monocyte counts reported in OB subjects compared to non-OB controls, in addition to a higher proportion of monocytes of classical and intermediate phenotype.¹⁴ Leukocytes are also sensitive to the action of insulin; expression of the insulin receptor (insulin-R) has been reported in these cells, and in mice induced with IR by a high-fat diet, the development of IR in their peritoneal macrophages was observed, along with an “alternatively activated”, or M2 phenotype that reduced their ability to eliminate bacteria.^{15,16}

IR is a state that develops even in people with normal weight, and if this IR remains over time, it increases the probability of triggering multiple pathologies, including diabetes mellitus. In recent years, research has focused on studying the impact of the relationship between

the cells of the immune system, the metabolic alterations produced by obesity and diabetes mellitus; the aim of this study is to relate insulin resistance and monocyte count by nutritional status.

Methods

Analytical cross-sectional study, carried out from August 2022 to May 2023 in the adult population assigned to the Family Medicine Unit (FMU) no. 80 of the Mexican Institute of Social Security (IMSS) in Morelia, Michoacán, Mexico. Each patient was informed of the objective of the study verbally and was asked to sign a written informed consent letter.

Based on the observed proportions in direct antecedents of other research conducted by the Clinical Research group of the Biomedical Research Center in Michoacan (*Centro de Investigación Biomédica de Michoacán* (CIBIMI)), a sample size was calculated to evaluate the difference in proportions with a unilateral hypothesis test with a confidence level of 95%, obtaining 7.2 patients per study group. The sampling was non-probabilistic by convenience. The study population was IMSS beneficiaries of both genders aged 18 to 55 years. Pregnant women, chronic consumers of alcohol or tobacco, with a diagnosis of chronic diseases such as diabetes, arterial hypertension, autoimmune diseases, immunocompromised states, or with recent infections, or invasive surgical processes (two weeks prior to sampling) were not included.

The information was collected in a format designed by the researchers. In the first part, the patient's medical history was recorded with personal and hereditary pathologic antecedents, frequency of drug consumption, vaccination, among others. In the second

part, somatometry (weight, height, and body mass index [BMI]) was recorded to group patients into normal weight (NW), overweight (OW), and obese (OB). Bioelectrical impedance was performed with OMRON® HBF-514C digital body scales, following the guidelines of the equipment, which recommends wearing light clothing, without shoes or socks, with a straight back and arms stretched at a 90° angle to the body.

Peripheral blood samples were then taken from the patients, with a minimum fasting period of eight hours, for complete blood biometry, lipid and glucose profiles. The quantification of serum insulin was performed by ELISA technique, the identification of circulating monocytes and their subpopulations, and insulin-R expression density by flow cytometry, all these analyses were performed in the CIBIMI research laboratory. After obtaining the report of serum glucose, and insulin, the HOMA index was formulated using a cut-off point ≥ 2.5 ,¹⁷ which subdivided the three groups previously obtained by BMI into: without insulin resistance (NO-IR) and with insulin resistance (IR).

The Kolmogorov-Smirnov test was performed to identify the normality of the data. The results were expressed as mean or median and their respective dispersion measures, depending on the normality or non-normality of the data distribution. For the contrast between groups, the Kruskal-Wallis nonparametric test was used. In addition, Dunn's multiple comparison test was performed as a post-hoc test. Statistical significance was considered with a $p < 0.05$. All results were processed in the SPSS v. 23 and Prisma 7.0 package.

The study was evaluated and approved by the IMSS Local Health

Research and Ethics Committee (R-2022-1602-020).

Results

Forty-five people participated, who were classified according to their BMI as obese (OB, $n = 15$), overweight (OW, $n = 11$), and normal weight (NW, $n = 19$). These were subsequently sub-grouped according to their HOMA-RI index into: OB-IR ($n = 13$), OB ($n = 2$), OW-IR ($n = 6$), OW ($n = 5$), NW-IR ($n = 12$), NW ($n = 7$) (Table 1).

When comparing the groups using the Kruskal-Wallis test, significant differences were observed in anthropometric parameters such as weight ($p = 0.0001$), BMI ($p = 0.0001$), body fat percentage ($p = 0.0001$), visceral fat ($p = 0.0001$), and waist circumference ($p = 0.0001$). These differences are explained by the composition of the study groups based on BMI category.

When stratifying the frequency of IR among the study groups, it was observed that 42% of the normal weight participants presented IR. This highlights the importance of a history of IR even in the lean, and clinically healthy Mexican population (Figure 1).

When evaluating the number of circulating monocytes between the groups of patients studied, no statistical difference was found in the number of monocytes in subjects with IR compared to their non-insulin resistant counterparts (Figure 2A). Similarly, when analysing the different phenotypes of circulating monocytes, there was no significant statistical difference in the number of classical (Figure 2B), intermediate (Figure 2C) and non-classical (Figure 2D) monocytes in patients with IR compared to their non-IR counterparts.

Table 1. Clinical, Anthropometric, and Biochemical Variables of the Participants

Variable	OB – IR n= 13	OB n= 2	OW – IR n= 6	OW n= 5	NW - IR n= 12	NW n= 7	P
Age (years)	31 22-56	36.5 36-37	28.5 25-34	29 28-48	29 25-47	27 25-38	0.486
Weight (kg)	94.3 75.6-122.4	93.95 91.8-96.10	76.1 64-86	75.2 60-90	62.6 50-83.60	68.8 52.50-80	0.0001
Size (m)	1.64 1.51-1.80	1.68 1.67-1.69	1.64 1.52-1.76	1.63 1.53-1.88	1.66 1.50-1.85	1.73 1.48-1.87	0.598
BMI (kg/m ²)	36.9* 30.68-40.0	33.27 32.90-33.65	27.7 25.5-29.9	26.20 25-29.30	23.53 18.82-24.78	23.46 18.68-24.60	0.0001
BF (%)	48.75* 38.80-52.80	35.10 34.10-36.10	34.80 26.2-47.3	29.8 23.9-47.8	29.85 22.80-39.40	26.60 12.90-39.30	0.001
LM (%)	23.25 21-35	31 30-32	24.10 19-36	25.70 21-28	26.65 22-38	28.10 23-43	0.168
Visceral Fat (%)	10.50* 7-19	17 17	7 6-9	6 5-9	5 3-8	6 2-6	0.0001
Waist (cm)	100.5* 7-19	105.50 101-110	85 73-106	94 77-102	80.50 69-84	77 75-94	0.0001
Glucose (mg/dL)	97 80-120	91.5 90-93	90 82-103	100 88-126	92 77-107	91 68-96	0.176
TC (mg/dL)	189 127-249	211.5 190-233	188.5 143-213	197 153-223	170 115-239	147 113.178	0.078
HDL-c (mg/dL)	43 32-51	39 38-40	65 36-75	55 47-63	55 22-92	52.50 35-70	0.687
LDL-c (mg/dL)	121 53.6-149	111.7 88.2-135.2	110 103-117	102.7 81.4-124.0	80.80 68-110	93.40 91.20-99.5	0.322
VLDL-c (mg/dL)	47.9 39.4-56.4	33.7 20.8-46.6	19.6 12-27	30.50 9-52	18.30 15-21.60	19.2 11-31	0.418
TG (mg/dL)	152 91-921	200.5 104-297	113 60-199	91 43-260	99 61-269	96 50-155	0.065
INSULINE (μUI/mL)	21.53* 11.3-103.0	9.19 8.29-10.10	14.71 11.8-39.18	7.35 5.51-9.59	14.46 11.18-54.94	10.12 7.65-11.12	0.0001
HOMA-IR	4.46* 2.69-26.21	2.08 1.84-2.32	3.28 2.54-8.90	2.06 1.36-2.13	3.35 2.57-12.89	2.07 1.70-2.50	0.0001

OB: Obesity, OW: Overweight, NW: Normal Weight, IR: Insuline Resistance, BMI: Body Mass Index, BF: Body Fat, LM: Lean Mass, TC: Total Cholesterol, HDL-c: High-density Lipoprotein Cholesterol, LDL-c: Low-density Lipoprotein Cholesterol, VLDL-c: Very Low-density Lipoprotein Cholesterol, TG: Triglycerides. Kruskal-Wallis test with Dunn's multiple comparison test as post-hoc, p < 0.05.

Figure 1.

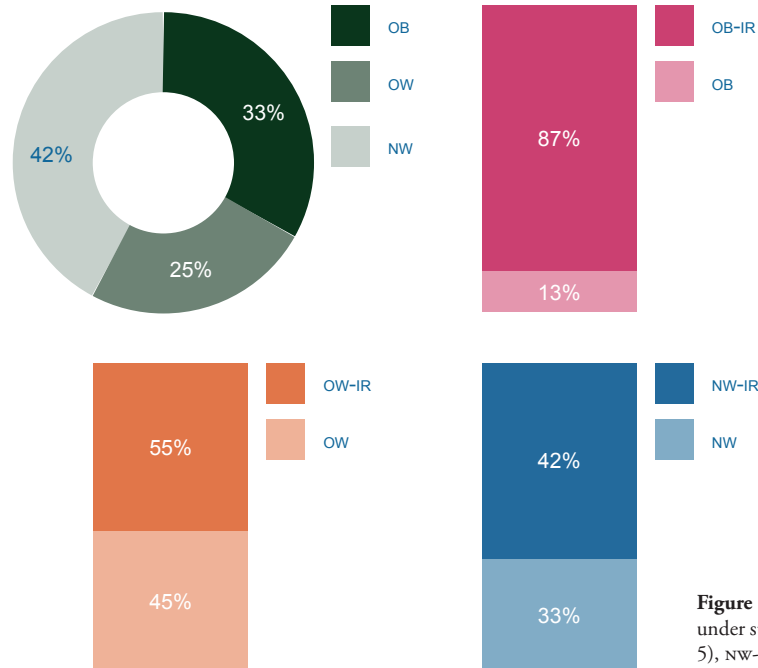


Figure 1. Frequency of insulin resistance in the patients under study. OB-IR (n= 13), OB (n= 2), OW-IR (n= 6), OW (n= 5), NW-IR (n= 12), NW (n= 7).

Figure 2.

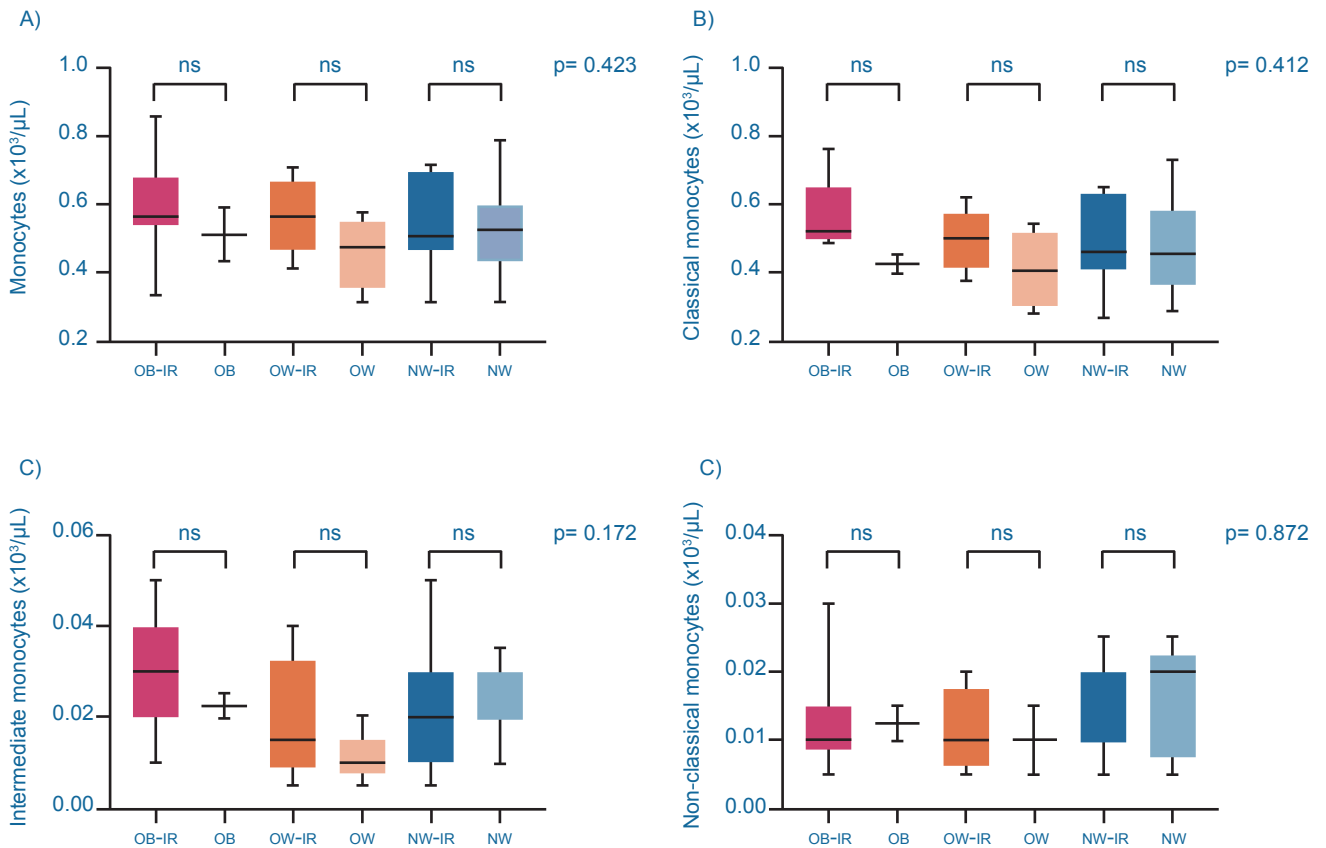


Figure 2. Count of monocytes and their subpopulations in the blood circulation of the patients under study. OB-IR (n= 13), OB (n= 2), OW-IR (n= 6), OW (n= 5), NW-IR (n= 12), NW (n= 7). Kruskal-Wallis test. $p < 0.05$.

Figure 3 shows the expression of the insulin receptor in different types of circulating monocytes of the subjects under study. No significant statistical difference was observed in the density of insulin receptor expression in monocytes. A) Monocytes; B) Classical monocytes; C) Intermediate monocytes; D) Non-classical monocytes.

Discussion

Obesity is a metabolic disease that affects a high percentage of the world's population.¹⁸ This pathology leads to a chronic proinflammatory state in which one of its

main effects is the development of insulin resistance at the cellular level, which in turn increases serum concentrations of this hormone,¹⁹ so in this study we analyzed the effect that this hyperinsulinemic state can have on the immune system, specifically on monocytes and their subpopulations, both in OB and non-OB patients. No statistically significant differences were found between the groups by nutritional status, monocyte type and IR.

In Mexico, figures from the National Health and Nutrition Survey (ENSANUT) 2021 showed a combined prevalence of OW and OB affecting about 7.5 out of 10

people.^{4,20} This data is concerning for the health of the Mexican population given that obesity is associated with a variety of chronic diseases.

It has been suggested that during OB, adipose tissue undergoes a process of homeostatic remodeling to counteract the pathophysiological effects of high dietary intake, whereby both adipose, and immune cells infiltrating the adipose tissue alter their cytokine production profile and induce a process of lipoinflammation, which has been closely linked to the decrease in peripheral insulin sensitivity.^{21,22}

Figure 3.

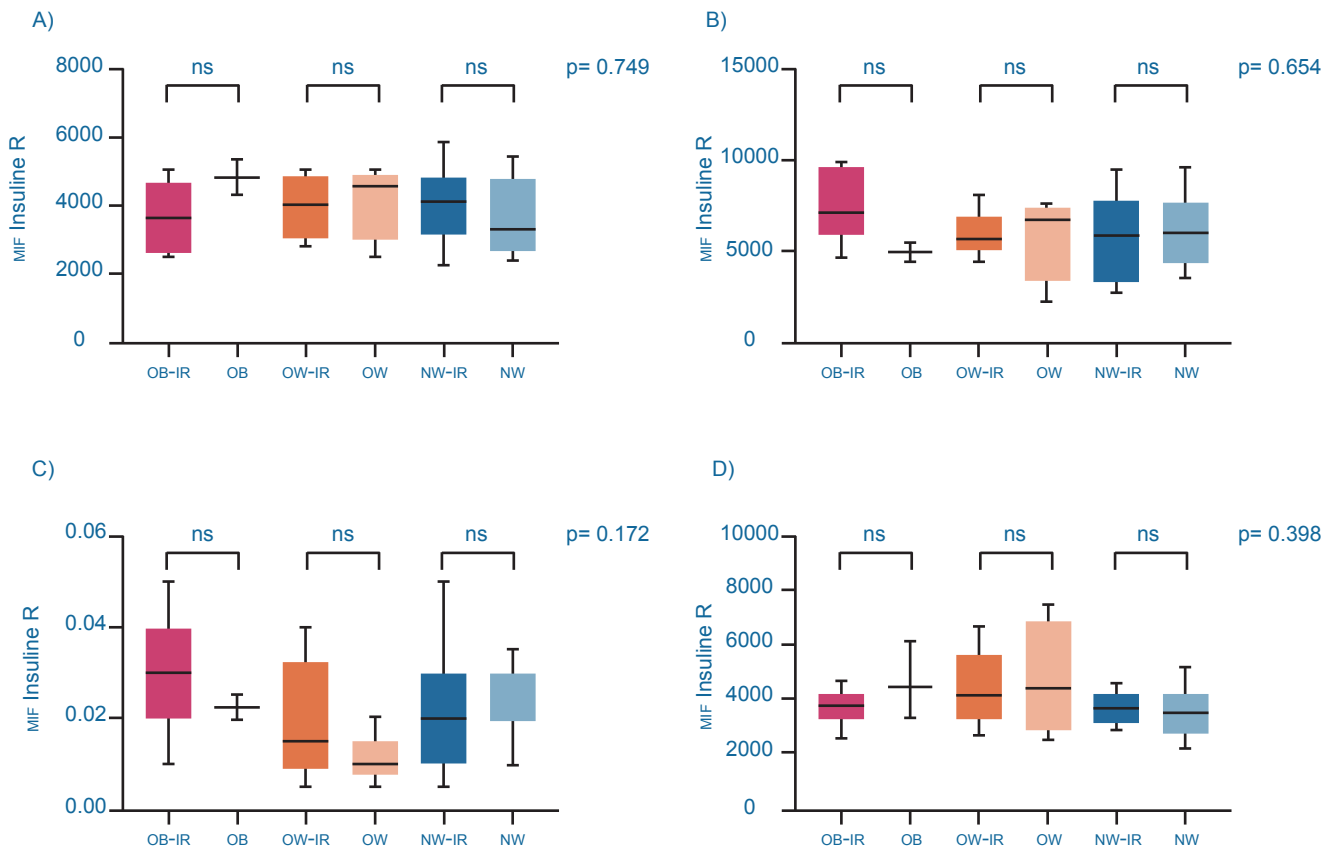


Figure 3. Insulin receptor expression in circulating monocytes and their subpopulations of the patients under study. OB-IR (n= 13), OB (n= 2), OW-IR (n= 6), OW (n= 5), NW-IR (n= 12), NW (n= 7). Kruskal-Wallis test. $p < 0.05$.

On the other hand, insulin is a hormone that promotes post-absorptive metabolism in the organism, facilitating the entry of glucose into insulin-dependent tissues; however, constant exposure to high levels of insulin decreases the capacity to transduce signals from its receptor, promoting systemic states of “insulin resistance”, which compromise the cellular metabolic capacity in tissues sensitive to its effect.²³

Thus, when stratifying the frequency of IR among the groups under study, a significant proportion of this metabolic phenomenon was observed among subjects with normal weight (26.7%), which highlights the importance of its dissemination even among the thin and clinically healthy Mexican population. Although these findings differ from those reported by Sejooti et al,²⁴ for the Asian population, who reported 37.1% of IR in metabolically obese lean subjects, they highlighted the high insulinemia figures ($18.35 \pm 11.76 \mu\text{IU/mL}$) present in our patients, which were considerably higher than those reported for this other Bangladeshi population ($11.1 \pm 4.9 \mu\text{IU/mL}$).

In addition, it has been described that there are three main subpopulations of monocytes that are closely related to the chronic inflammatory process characteristic of obesity, classified as: classical ($\text{CD14}^{++}\text{16}^{-}$), intermediate ($\text{CD14}^{++}\text{16}^{+}$), and non-classical ($\text{CD14}^{+}\text{16}^{++}$).²⁵ These cells differ mainly in their ability to secrete different profiles of pro- and anti-inflammatory cytokines, reflecting their cellular functionality as well as their capacity for immune response to environmental challenges.²⁶ It has been reported that the circulating proportion of these monocytes may be affected under OB

conditions, with higher total monocyte counts reported in OB subjects, as well as higher proportions of classical and intermediate phenotype monocytes in these patients.²⁷

When evaluating the numbers of monocytes in blood circulation between the groups of patients under study, no difference was found in the monocyte count between the groups of IR subjects compared to their counterparts without IR, probably due to the influence of the sample size for each study group.

To the best of our knowledge, there are no reports in the literature that refer to the relationship between monocyte subpopulation counts in the Mexican adult population with IR, so the present finding is useful because it establishes a precedent for the characterization of the immune cells involved in the IR processes that develop as part of those that occur in the progression to OB.

In addition, it is known that IR affects the expression of the insulin receptor in circulating monocytes from OB patients,²⁸ but in this study, it was not observed a higher density of expression in monocytes from NW-IR, OW-IR, and OB-IR subjects. It is likely that the acquisition of an insulin resistance phenotype in these immune cells is not manifested in the amount or expression of the insulin receptor, but at the intracellular level, and that its effects on the response mechanisms of the immune system have been little studied.

Among the strengths of this study is the detection of insulin resistance in normal weight individuals. This study opens the opportunity for further research on the influence of IR on the immune system, specifically on the different subpopulations of monocytes and at the intracellular level, given the

importance of the relationship between inflammation and obesity.

Among the limitations of this investigation, there is the difficulty in recruiting patients with the characteristics of each study group. This situation was specific in the group with OB, OW, and NW without IR. The study sample in each group may be an underrepresentation of the population that could be affected by IR. This is relevant given the unknown presence of IR in the eligible population. This recruitment difficulty limits the generalizability of the study results and highlights the need for further studies to increase the sample size, and to emphasize to primary care physicians the importance of detecting and treating insulin resistance, especially in populations that may be unaware of their metabolic health status, such as normal weight subjects.

Conclusions

The presence of systemic IR was described in patients with favorable nutritional status or normal weight. While, in patients with IR, no difference was observed in the total monocyte count and its subpopulations, nor in the expression of its insulin receptor. Therefore, it is proposed the basis for future analyses on the influence of IR on intracellular signaling and secretion of proinflammatory cytokines derived from different monocyte subtypes of patients with and without insulin resistance. At the clinical level, screening is recommended not only in those with altered nutritional states, but also in a clinically healthy thin population, in order to address the pathology in early periods that allow patients to restore their innate immune system, thus preventing adverse clinical outcomes.

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Authors' Contributions

All authors contributed to the development, design, implementation, and writing of this study.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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