Insulin Resistance Syndrome in the Elderly

Assessment of functional, biochemical, metabolic, and inflammatory status

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OBJECTIVE — Hyperinsulinemic euglycemia, or insulin resistance syndrome (IRS), is associated with increased morbidity and mortality. Although thought to be associated with proinflammatory states, little work has been done in this area. Here, we determined the impact of IRS on functional, biochemical, metabolic, and inflammatory status in a high-risk population: elderly women in nursing homes.

RESEARCH DESIGN AND METHODS — Functional, biochemical, metabolic, and inflammatory parameters were measured in 100 consecutive ambulatory, elderly women who resided in nursing homes. Diabetic subjects and residents with fasting blood glucose ≥110 mg/dl were excluded. Remaining residents were classified as insulin resistant (IR) (insulin >100 pmol/l) or non-IR (NIR).

RESULTS — A total of 16 residents were IR and 53 NIR. No differences in functional status, BMI, renal function, C-reactive protein, or immune cell levels were found. Fasting blood glucose was higher in IR subjects ([means ± SD] 94.1 ± 8.1 vs. 87.9 ± 8.2, $P < 0.05$), indicating a very mild glucose intolerance. Serum C-peptide ($P < 0.05$), amylin ($P < 0.01$), and leptin ($P < 0.01$), but not adiponectin or resistin, were higher in IR subjects. Higher leptin-to-BMI and insulin–to–C-peptide ratios suggested an increased percent body fat mass and altered clearance of insulin, respectively. Eleven of 13 cytokines had arithmetic elevations, but only tumor necrosis factor-α (TNF) reached statistical significance ($P < 0.01$). TNF and insulin levels were highly correlated.

CONCLUSIONS — IRS in the healthiest of long-term care residents is relatively rare but is associated with mild glucose intolerance, increased percent body fat, altered insulin clearance, and a proinflammatory status as evidenced by an elevated TNF.

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Insulin resistance syndrome (IRS) is characterized by a decreased tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion (1). It is thought that most adults with IRS maintain normal glucose levels and will never develop overt type 2 diabetes but are nonetheless at increased risk for cardiovascular disease. Whereas diabetes is defined on the basis of serum glucose levels regardless of insulin status, IRS is defined on the basis of serum insulin levels regardless of glucose status. The population of IRS that clearly does not overlap with diabetes is that with euglycemic hyperinsulinemia. Residents with IRS, despite euglycemia, are at increased risk for hypertension, stroke, polycystic ovary syndrome, and nonalcoholic steatohepatitis (2).

Because measuring serum insulin is not part of routine clinical practice, diagnosing IRS is difficult. As such, diagnosis is often made based on the presence of secondary criteria, such as hypertension, history of glucose intolerance, or elevated BMI (2). As these are also associated with diabetes and likely are sequella developing from IRS, such a diagnostic approach makes it difficult to ascertain incidence of IRS or to study early pathological events that may be unique to it. These difficulties are magnified in the elderly, as many of the secondary criteria are independently associated with aging.

Here, we studied a population of elderly, ambulatory women living in long-term care facilities in a Midwestern metropolitan area. We assessed in the euglycemic subset their functional, biochemical, metabolic, and inflammatory parameters as a function of endogenous serum insulin levels.

RESEARCH DESIGN AND METHODS

— Studies were approved by the local institutional review board, and consent forms were obtained on all participants. One hundred elderly ambulatory women aged ≥65 years were recruited from eight long-term care facilities in the St. Louis metropolitan area. Exclusion criteria for the study were nonambulatory status or a contraindication for exercise. A fasting morning blood sample was drawn and measured for glucose, electrolytes, blood urea nitrogen, creatinine, blood urea nitrogen–to–anion gap ratio, anion gap, C-reactive protein, prealbumin, albumin, transferrin, white blood cells (further assessed as percentages of neutrophils, lymphocytes, eosinophils, and segments), platelets, red cell indexes, and hemoglobin. Blood samples were also measured blinded with multiplex kits (Millipore, St. Charles, MO) for insulin, C-peptide, leptin, total amylin, adiponectin, resistin, interleukin (IL)-1α, IL-1β, IL-1 receptor antagonist, IL-2, IL-4, IL-6, IL-8, IL-10, interferon-γ, tumor necrosis factor (TNF)-α, eotaxin, macrophage inflammatory protein (MAP)-1α, and regulated on activation, normal T-cell expressed and secreted (RANTES). Any multiplex levels above the detection limit were diluted and assayed again. Any multiplex levels below

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Abbreviations: IL, interleukin; IR, insulin resistant; IRS, insulin resistance syndrome; MAP, macrophage inflammatory protein; NIR, non–insulin resistant; RANTES, regulated on activation, normal T-cell expressed and secreted; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Resident characteristics*

	IR group	NIR group	*P*
n	16	53	
Age (years)	81.9 ± 6.8	83.8 ± 6.6	0.43
Height (cm)	155.7 ± 5.5*	156.7 ± 7.3	0.61
Weight (kg)	65.6 ± 9.3*	62.3 ± 13.5	0.20
BMI (kg/m^2)	26.6 ± 2.9*	25.1 ± 5.3	0.09
Charlson index score	2.8 ± 0.8	2.9 ± 1.4	0.89
Smoker status			0.6
Current smoker	0 (0)	3 (6)†	
Never smoked	5 (31)	14 (28)	
Former smoker	11 (69)	33 (66)	
Consumes alcohol	0 (0)	10 (20)†	0.052
Mini–mental state examination	22.3 ± 6.4*	21.4 ± 7.2‡	0.82
Functional independence measure	99.4 ± 20.4	94.2 ± 20.6	0.23
Mini–nutritional assessment	21.1 ± 4.1‡	21.7 ± 4.4	0.77
ADL	12.2 ± 4.1	12.8 ± 4.5	0.79
GDS	8.5 ± 7.0†	7.1 ± 5.2§	0.65
Get-up-and-go test	30.6 ± 21.4†	32.7 ± 18.2‖	0.31
At 6 meters	13.9 ± 6.7†	17.4 ± 14.4§	0.39
At 6 min	148.9 ± 34.2‡	138.8 ± 67.9¶	0.45

Data are means ± SD or *n* (%). *Based on $n - 1$. †Based on $n - 3$. ‡Based on $n - 2$. §Based on $n - 5$. ‖Based on $n - 7$. ¶Based on $n - 13$. ADL, activities of daily living; GDS, geriatric depression scale.

the detection limit were assigned the value of 1.0. Residents were weighed, their height measured, and their BMI calculated as weight (in kilograms) divided by the square of height (in meters). Mini–mental status examination (3), mini–nutritional assessment (4), activities of daily living (5), the geriatric depression scale (6), functional independence measures (7), the comorbidity scale of Charlson (8,9), the timed get-up-and-go test (10), the timed 6-m walk (11), the 6-min walk (12), smoking history, and alcohol consumption history were assessed at the time of enrollment.

Residents on any form of medication for the treatment of diabetes or with a fasting blood glucose of ≥110 mg/dl were excluded from further analysis. One resident with abnormally high values for C-peptide (>4,500 pmol/l), insulin (2,280 pmol/l), and total amylin (>4,500 pmol/l) was excluded from the study. The 69 remaining nondiabetic, euglycemic residents were classified as insulin resistant (IR) (fasting serum insulin >100 pmol/l, $n = 16$) or non-IR (NIR) (fasting serum insulin <100 pmol/l, $n = 53$).

Two inflammatory scores were calculated by first determining the median values for a parameter and then calculating the number of subjects who had values higher than the median. The first inflammatory score included the parameters of C-reactive protein, TNF, IL-6, and IL-1β, and values ranged from 0 to 4. The second inflammatory score excluded C-reactive protein for a measure based entirely on cytokine measures.

Analysis of data

Means are reported with their SDs and *n*. Results were analyzed using the SPSS version 14 package. IR and NIR subjects were compared using χ^2 tests for categorical variables and Mann-Whitney *U* tests for continuous variables. Rank-order correlations (Spearman's *r*) were used to investigate associations. Statistical significance was determined at the 0.05 level and statistical trend defined as $0.05 < P < 0.10$.

RESULTS — The mean insulin levels were 280 ± 313 pmol/l (IR group, $n = 16$) and 58.4 ± 18.51 pmol/l (NIR group, $n = 53$). Table 1 compares resident characteristics. There were no differences in age, morphometric measures, or functional, nutritional, or mental status, although there was a statistical trend ($P = 0.09$) toward an elevated BMI in the IR group. Table 2 shows that glucose was slightly elevated in the NIR group ($P < 0.05$), but there were no differences in the other general chemistries. Renal function as measured by creatinine or the blood urea nitrogen–to–creatinine ratio was similar between the two groups.

C-peptide ($P < 0.05$), amylin ($P < 0.001$), and leptin ($P < 0.01$) were all elevated in the IR group (Table 2). Adiponectin showed a statistical trend ($P = 0.08$) toward being lower in the IR group. The proinflammatory cytokine TNF was ~50% higher ($P < 0.01$) (Table 2); although the other cytokines except for MIP-1α and RANTES were arithmetically higher in the IR group, none reached statistical significance. C-reactive protein, immune cell measures, and neither of the proinflammatory indexes were significantly different between the IR and NIR groups.

Ratios of leptin to BMI ($P < 0.01$), insulin to C-peptide ($P < 0.001$), insulin to BMI ($P < 0.001$), and insulin to TNF ($P < 0.001$) were significantly higher in the IR group (Table 3). The ratios for insulin to leptin, TNF to BMI, and insulin to amylin were not different between the two groups.

Significant positive correlations were found between BMI and leptin ($P < 0.001$, $r = 0.68$), TNF and insulin ($P < 0.01$, $r = 0.36$), leptin and insulin ($P < 0.01$, $r = 0.31$), and insulin and the leptin-to-BMI ratio ($P < 0.01$, $r = 0.34$). Figure 1 shows the relation between TNF and log insulin ($Y = 9.21x + 5.36$, $r = 0.533$, $n = 69$, $P < 0.01$). Adiponectin and leptin were inversely correlated ($P < 0.001$, $r = -0.50$). There were trends for associations between C-reactive protein versus TNF ($P = 0.07$) and insulin versus BMI ($P = 0.06$). TNF and leptin did not correlate.

CONCLUSIONS — IRS is increasingly recognized as a harbinger of classical disease states, including diabetes and metabolic syndrome X. It has been postulated that insulin resistance, diabetes, and metabolic syndrome X are all associated with a proinflammatory state, but it has been difficult to determine whether the proinflammatory state is a cause or effect of these conditions. Furthermore, it is unclear what proinflammatory cytokines are most likely to be elevated early in the course of these conditions, especially in insulin resistance. All these conditions also become increasingly common with aging. Here, we examined functional, chemical, metabolic, and inflammatory status in a relatively healthy and uniform population of elderly women. We excluded any person taking diabetes medications and used strict criteria for euglycemia (i.e., fasting glucose <110 mg/dl).

These residents had significant impairments in their abilities to care for themselves, requiring nursing home

Table 2—*Laboratory values in IR and NIR subjects*

	IR group	NIR group	*P*
n	16	53	
Insulin (pmol/l)	280.1 ± 312.5	58.4 ± 18.5	<0.001
Na (mmol/l)	139.5 ± 2.9	140.3 ± 2.8	0.45
K (mmol/l)	4.2 ± 0.3	4.4 ± 0.4	0.14
Cl (mmol/l)	104.7 ± 3.3	104.1 ± 4.6	0.67
CO_2 (mmol/l)	25.8 ± 2.2	27.1 ± 3.0	0.08
BUN (mg/dl)	16.1 ± 3.9	19.1 ± 7.0	0.27
Creatinine (ng/dl)	0.9 ± 0.2	0.9 ± 0.3	0.79
Ca (mg/dl)	9.2 ± 0.5	10.9 ± 12.6	0.89
Cholesterol (mg/dl)	189.6 ± 37.3	193.4 ± 46.9*	0.86
Agap (mmol/l)	13.3 ± 3.7	13.6 ± 3.6	0.63
BUN/creatinine	18.5 ± 7.2	20.6 ± 6.2	0.19
PreA (mg/dl)	21.7 ± 4.9	21.6 ± 6.0	0.72
Albumin (g/dl)	3.4 ± 0.4	3.4 ± 0.4*	0.95
Transferrin (mg/dl)	230.1 ± 33.7	229.3 ± 50.3	0.90
C-reactive protein (mg/dl)	0.5 ± 0.4	0.9 ± 1.9	0.40
WBC (k/mm^3)	6.8 ± 2.3	6.1 ± 1.7	0.38
RBC (m/mm^3)	4.2 ± 0.4	4.0 ± 0.6	0.19
HGB (g/dl)	13.0 ± 0.9	12.2 ± 1.4	0.11
HCT (%)	38.7 ± 3.0	36.7 ± 4.2	0.13
PLT (k/mm^3)	238.8 ± 48.0	249.9 ± 68.9	0.78
MPV (fl)	8.6 ± 1.1*	9.0 ± 1.1†	0.10
MCV (fl)	91.5 ± 3.1	91.5 ± 6.2	0.96
MCH (pg)	30.7 ± 1.1	30.6 ± 2.4	0.80
MCHC (g/dl)	33.5 ± 0.8	33.4 ± 0.9	0.59
RWD (%)	14.1 ± 1.3	14.9 ± 2.2	0.19
Neutro (%)	55.8 ± 9.6	58.7 ± 9.1	0.17
Lymph (%)	31.4 ± 7.9	28.2 ± 8.3	0.18
Mono (%)	8.1 ± 1.8	9.0 ± 2.6	0.21
Eos (%)	4.4 ± 3.1	3.5 ± 3.0	0.17
Baso (%)	0.7 ± 0.3*	0.6 ± 0.4†	0.11
IL-1β (pg/ml)	12.9 ± 24.0	6.2 ± 21.4	0.44
IL-2 (pg/ml)	47.8 ± 109.2	10.4 ± 20.9	0.49
IL-1rα (pg/ml)	333.3 ± 478.3	187.3 ± 226.2	0.15
IL-4 (pg/ml)	563.7 ± 1,379.2	318.0 ± 861.6	0.10
IL-6 (pg/ml)	186.2 ± 355.8	67.8 ± 118.3	0.94
IL-8 (pg/ml)	76.7 ± 105.0	43.8 ± 66.6	0.30
IL-10 (pg/ml)	30.9 ± 66.0	21.2 ± 82.4	0.18
IL-1α (pg/ml)	310.4 ± 852.6	218.1 ± 560.2	0.89
Interferon-γ (pg/ml)	7.3 ± 14.4	2.6 ± 3.4	0.66
TNF-α (pg/ml)	15.3 ± 6.6	10.8 ± 4.6	0.008
Eotaxin (pg/ml)	173.3 ± 105.7	151.4 ± 58.9	0.87
MIP-1a (pg/ml)	39.7 ± 70.8	49.4 ± 87.3	0.32
RANTES (pg/ml)	39,264.0 ± 17,184.7	39,952.8 ± 16,926.6	0.92
Leptin (pmol/l)	2,828.2 ± 1,961	1,675.6 ± 1,722.5	0.005
T-Amylin (pmol/l)	34.6 ± 58.1	8.0 ± 7.2	<0.001
C-peptide (pmol/l)	721.0 ± 378.5	628.0 ± 714.2	0.03
Adiponectin (ng/ml)	29,796.2 ± 17,293.5	40,151 ± 21,827.2	0.08
Resistin (pg/ml)	13,801.1 ± 3,493.8	15,918.6 ± 13,289.1	0.53
Glucose (mg/dl)	94.1 ± 8.4	87.9 ± 8.2	0.02

Data are means ± SD. *Based on $n - 1$. †Based on $n - 2$. Agap, anion gap; Baso, basophil; BUN, blood urea nitrogen; Eos, eosinophil; Lymph, lymphocyte; MIP, macrophage inflammatory protein; Mono, monocytes; Neotro, neutrophil; PreA, prealbumin; T-amylin, total amylin.

placement. They were, however, the healthiest members of the nursing home population, having on average mild to moderate cognitive and functional impairments. Mean insulin levels were 280 pmol/l in the IR group and 58.4 pmol/l in the NIR group. It is significant that the majority of recruited residents did not have IRS, fasting hyperglycemia, or frank diabetes, as it is generally assumed that residents this debilitated would have near-universal insulin resistance (13).

Those with IR did not differ from the NIR group in age, height, weight, smoking history, drinking history, or nutritional risk, as measured by the mini–nutritional assessment tool. Importantly, the two groups did not differ in BMI, although the IR group had a BMI that was ~6% greater ($P = 0.09$). The groups did not differ on measures of severe illness as measured by the comorbidity scale of Charlson, a medical record–based inventory of 19 conditions associated with inpatient mortality. Functional status did not differ between the two groups, as measured by four different measures: the functional index measure, the activities of daily living, the 6-m walk, and the 6-min walk. This lack of difference suggests that the muscle wasting, sarcopenia, and frailty associated with insulin resistance (13) is confounded by aging and other associated factors and is more likely a later association with IRS. Levels of depression, as measured by the geriatric depression scale, or dementia, as measured by the mini–mental status examination, were similar between the groups. Balance and risk of falls as measured by the timed get-up-and-go test was also similar. This lack of difference shows that any deleterious effects of insulin resistance had not yet manifested themselves in common indexes of health status.

These groups did not differ in the indicators of general inflammation, including C-reactive protein, prealbumin, albumin, transferrin, or immune cell levels, or in hemoglobin or hematocrit. They also did not differ in cholesterol levels. Hyperlipidemia is a hallmark of metabolic syndrome X, whereas low cholesterol (<160 mg/dl) is used in geriatrics as an index of malnutrition. Overall, therefore, insulin resistance had little impact on immediate general health, giving us the opportunity to examine an early stage of IRS.

Although the study included only those with a fasting blood glucose of <110 mg/dl, glucose was higher ($P < 0.05$) in the IR (94.2 mg/dl) versus the NIR group (87.9 mg/dl). The IR group fasting glucose was well within normal limits and only 7% higher than in the NIR group. Nevertheless, it is a clear indication that even this early stage of IRS is associated with impairments in glucose handling.

In contrast to the lack of differences in

Table 3—*Ratios*

	IR group	NIR group	*P*
n	16	53	
Leptin to BMI	106.3 ± 67.2*	62.4 ± 59.0	0.002
TNF-α to leptin	0.01 ± 0.02	0.02 ± 0.02	0.11
Insulin to C-peptide	0.6 ± 0.7	0.1 ± 0.1	<0.001
Insulin to leptin	0.2 ± 0.3	0.1 ± 0.2	0.11
Insulin to BMI	9.2 ± 10.3*	2.4 ± 0.9	<0.001
Insulin to TNF-α	17.1 ± 14.2	6.4 ± 3.8	<0.001
TNF-α to BMI	0.5 ± 0.2*	0.4 ± 0.2	0.14
Insulin to amylin	35.3 ± 101.9	20.1 ± 21.5	0.87

Data are means ± SD. *Based on $n - 1$.

routine laboratories, several hormone levels were elevated in the IR group. As expected, insulin C-peptide was elevated but only by ~15%. Interestingly, the insulin/C-peptide level was about fivefold higher in the IR group, suggesting that insulin or C-peptide clearance or degradation was affected more than secretion. Any difference in insulin clearance cannot be ascribed to renal failure, as serum creatinine did not differ between the IR and NIR groups. Amylin, cosecreted with insulin in a 1:1 molar ratio from the pancreas, was also elevated over fourfold in the IR population. The ratio of insulin and amylin did not differ between the two groups, suggesting that the two peptides were cleared and secreted in a similar fashion.

Serum insulin levels were highly correlated with serum leptin levels, consistent with insulin resistance being associated with obesity. As expected from numerous other studies, leptin also correlated positively with BMI and inversely with adiponectin. Leptin was increased ~70% in the IR population ($P < 0.01$). This was unexpected, given that the average BMI for the IR group was only marginally (6%), and not significantly, higher than in the NIR group. However, BMI is a cruder measure of adiposity than serum leptin, as BMI does not distinguish between lean and adipose tissue. The leptin-to-BMI ratio was also ~70% higher in the IR group in comparison with the NIR group ($P < 0.005$). This suggests that either those in the IR group were hypersecreting leptin per unit of fat mass or that a greater percent of their body weight was adipose tissue. The latter seems more likely, considering the recent description of the sarcopenic obese. These residents, despite having a normal or high BMI, have decreased muscle mass, and so a greater proportion of their BMI is adipose tissue. Such residents are at an increased risk for mortality and morbidity. The current findings suggest that insulin resistance could be an early component of sacropenic obesity.

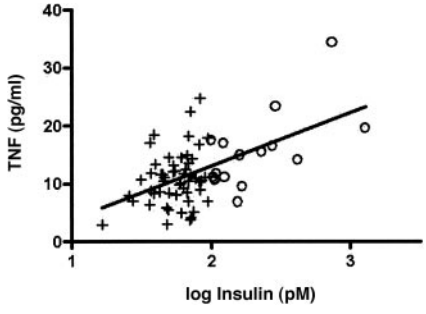

Figure 1—*TNF and insulin. A nonlinear relation existed between serum levels of TNF and serum levels of insulin. **P < 0.01. +, NIR group; ○, IR group.*

The strong associations of leptin and leptin/BMI with serum insulin and their segregation between the NIR and IR groups suggest a strong association between obesity and insulin resistance. However, BMI only showed a trend toward association with insulin ($P = 0.06$), whereas the leptin-to-BMI ratio correlated better with serum insulin than did leptin alone. This again suggests that serum levels of leptin are much more sensitive at inventorying the metabolic parameters associated with insulin resistance than is BMI. This is further suggested by the finding that the leptin-to-insulin ratio did not differ between the IR and NIR groups, even though each of these components alone were very different. Thus, leptin and insulin overlap to some degree in their abilities to distinguish the IR and NIR groups but likely retain independent predictive abilities.

In contrast, serum adiponectin levels correlated even more strongly with leptin than did insulin. Adiponectin is secreted from fat and can reverse insulin resistance and hyperglycemia, possibly through its ability to regulate proinflammatory cytokines (14–17). However, adiponectin did not distinguish insulin resistance from non–insulin resistance, being decreased in the IR group by ~25% ($P = 0.08$).

Evidence for a proinflammatory state was most clearly revealed by a significant ($P < 0.01$) elevation in TNF. TNF levels were 50% higher in IR compared with NIR residents. Arithmetic increases that did not reach statistical significance were evident in every other proinflammatory and anti-inflammatory cytokine measured with the exceptions of MIP-1α and RANTES. The lack of statistical significance in the elevations of some of the cytokines may have been caused in part by the large variance within groups. To further assess a global trend of cytokine elevation and to negate variance, we computed two proinflammatory indexes, both of which included TNF that assessed elevations on nonparametric scoring. However, neither of these summations was different between the two populations. This suggests that even with the power of including a statistically significant component (TNF), there is no evidence for a statistically meaningful global cytokine increase. This supports TNF as being the primary cytokine whose elevation is relevant in early insulin resistance.

The role of serum TNF is further supported by a strong correlation with serum insulin levels. This correlation between TNF and insulin was even stronger than that between leptin and insulin. One source of serum TNF could be from adipose tissue. However, serum TNF levels did not correlate with serum leptin levels. In some studies, TNF and leptin levels correlate, presumably because both can be secreted from fat. However, TNF has sources in addition to adipose tissue, whereas adipose tissue is essentially the sole source of serum leptin. Therefore, the lack of correlation between leptin and TNF suggests that the source of elevated TNF was not adipose tissue. Further supporting this were the findings that the TNF-to-BMI ratio did not distinguish between IR and NIR groups the way leptin-to-BMI ratio did, and the TNF-to-insulin ratio, unlike the leptin-to-insulin ratio, still distinguished the IR and NIR groups. Therefore, TNF and leptin behaved very differently, making it unlikely that adipose tissue was the source of the elevation in TNF. TNF did show a statistical trend with C-reactive protein ($P = 0.07$), sug-

gesting that it might have arisen from a generalized proinflammatory condition.

In conclusion, we examined early insulin resistance in a population of elderly women living in a long-term care facility before debility ascribable to insulin resistance had arisen. Although no functional impairments were found between the IR and NIR groups, we found that other parameters were already changing. Despite exclusion of any person with a serum fasting glucose ≥110, a slight, statistically significant increase in serum glucose of 7% demonstrated an early glucose intolerance in the IR group. Differences in C-peptide and the insulin–to–C-peptide ratio suggested an increased insulin secretion and a decreased insulin clearance in the IR group. Increased leptin and leptin-to-BMI ratios in the absence of differences in BMI suggest that the IR group had a higher percent of body fat mass and that IR could be related to sarcopenia of obesity. TNF was the one proinflammatory cytokine statistically elevated in the IR group. The lack of correlation of TNF with BMI or leptin suggests that the TNF did not originate from fat. Thus, early insulin resistance is associated with elevations of leptin, even after correction of BMI and a proinflammatory state, as evidenced by elevated levels of serum TNF.

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