Correlation of HOMA-IR to Glycated albumin in centrally obese T2DM

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Abstract: Background: Insulin resistance as measured by Homeostasis Model assessment of insulin resistance (HOMA-IR) is the core pathophysiology of T2DM.It's correlation to intermediate glycemic index, glycated albumin (GA) can be linked to clinical parameters of the patients namely waist circumference which better expresses central obesity **Aim:** assessing the correlation of HOMA-IR to glycated albumin in centrally obese T2DM patients**. Hypothesis:** positive correlation exists between HOMA-IR &glycated albumin. **Subjects and methods**: Cross sectional study into which 62 participants- aged 25-60 years - who are T2DM on insulin were recruited at Suez Canal University hospital. None of them was smoker or known to be CLD or DKD patient, none was on regular statins, aspirin or metformin. All had normal CBC and albumin indices, they underwent thorough history taking & clinical examination, waist circumference and body mass index (BMI) were measured.They were grouped into a group with insulin resistance (29 patients) and group without insulin resistance (33 patients). FPG,PPPG, HbA1c, CBC, serum albumin, serum GA were analyzed.insulin resistance was measured by HOMA-IR.**Results**: GA was higher in centrally obese individuals with insulin resistance (622.1±166.6 µmol/L) than in centrally obese individuals without insulin resistance (568.3 ±169.2 µmol/L), GA former value was lower than GA in centrally non-obese with insulin resistance (686.2± 109.2 µmol/L), GA was higher in females with insulin resistance (632.1 ±173.9 µmol/L) compared to females without insulin resistance (543.1 ±146.0 µmol/L).**Conclusion:** This study showed that GA increase withHOMA-IR levels and female gender and decrease with increased waist circumference
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1. Introduction

Insulin resistance& Inflammation in disability:

Insulin resistance is found in all races, is generally considered to be higher among whites, ranging from 3-16% compared to less than 2% among Japanese populations. **(1, 2).**

The strongest relationship between insulin resistance &cardiovascular risk factors is observed in middle-aged men rather than in older individuals, Women tend to assume increased cardiovascular risk after menopause, overall cardiovascular morbidity & mortality increase with age. (**3**).

Type A insulin resistance typically occurs in younger patients, while type B occurs more often in older women. Insulin resistance can be due to hereditary causes including mutations of insulin receptor, glucose transporter, & signaling proteins **(1)** or acquired causes that include physical inactivity, unhealthy diet, medications, hyperglycemia (glucose toxicity), increased free fatty acids, &the aging process **(4).**

T2DM is characterized by increased hepatic glucose output, increased peripheral resistance to insulin action &impaired insulin secretion.**(5)** Insulin resistance and the compensatory hyperinsulinemia, &other components are associated with increased risk of cardiovascular disease; endothelial dysfunction is a prominent feature of insulin resistance syndrome **(6).**

Insulin sensitivity &secretion are reciprocally related; thus, insulin resistance results in increased insulin secretion to maintain normal glucose &lipid homeostasis. The mathematical relation between sensitivity & secretion is hyperbolic. Several mediators-include glucose, free fatty acids, autonomic nerves, fat-derived hormones (e.g, adiponectin), &the gut hormone glucagonlike peptide 1 (GLP-1) are thought to signal the pancreatic β cells to respond to insulin resistance; failure of the signals or of the B cells to adapt adequately in relation to insulin sensitivity results in inappropriate insulin levels, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), & type 2 diabetes. (**7).** Mitochondrial dysfunction may play an important role in the development of insulin resistance &associated complications. **(8).**

Inflammation &adipocytokines probably play some role in the etiopathogenesis of insulin resistance **(9-11).**

Increased levels of the acute-phase inflammatory marker C-reactive protein (CRP) are related to insulin resistance &the metabolic syndrome, suggesting a role for chronic, low-grade inflammation **(12).**

In a number of prospective studies, increased levels of CRP predicted the development of diabetes & cardiovascular disease.**(12-14)**

Obesity-associated insulin resistance is a major risk factor for type 2 diabetes &cardiovascular disease., a large number of endocrine, inflammatory, neural, &cell-intrinsic pathways have been shown to be dysregulated in obesity. Although it is possible that one of these factors plays a dominant role, many of these factors are interdependent, & it is likely that their dynamic interplay underlies the pathophysiology of insulin resistance **(15)**

Obese individuals develop resistance to the cellular actions of insulin, characterized by an impaired ability of insulin to inhibit glucose output from the liver &to promote glucose uptake in fat &muscle **(16).** The association between obesity &insulin resistance is likely a cause-and-effect relationship **(17, 18).**

A. Endocrine mechanisms:

1. Fatty acids (FAs):

Plasma FA concentrations are commonly elevated in obese individuals, mainly due to increased FA release associated with the expansion in fat mass **(19, 20)**. The notion that these FAs function as endocrine factors that regulate metabolic function in target tissues was first suggested >40 years ago, when **Randle *et al.* (1963)** hypothesized that obesity-associated insulin resistance could be explained by competition between these increased circulating FAs &glucose for oxidative metabolism in insulin-responsive cells.**(21)** Later, glucose uptake rather than intracellular glucose metabolism has been implicated as the rate-limiting step for FA-induced insulin resistance **(22).**

2.Adipokines:

Adipocytes also secrete metabolically active proteins**(23).**

2.a.Leptin is an adipocyte-secreted hormone whose absence leads to dramatic metabolic derangements **(24).**

*2.b*Adiponectin is specifically expressed in differentiated adipocytes **(25**). Its levels are low in obesity &administration of adiponectin improves insulin resistance in animal models **(26, 27)**

2. C Resistin was identified in 2001 as an adipocyte-specific secreted protein.**(28, 29).** It is elevated in rodent obesity, while infusion or sustained expression produces insulin resistance **(30).** Some studies show increased resistin expression &serum levels in association with obesity &insulin resistance **(31, 32).** Variant studies in humans show a consistent association between resistin&inflammation**(33, 34).**

2.d. Adipokines associated with inflammation.

Plasminogen activator inhibitor-1 (PAI-1)is the primary inhibitor of fibrinolysis by inactivating tissue-type plasminogen activator, expressed by adipocytes as well as stromal vascular cells in adipose depots **(35).** Plasma PAI-1 levels are elevated in obesity &insulin resistance &predict future risk for T2DM **(36)**.

Interleukin-6 (IL-6) is a cytokine that is closely associated with obesity &insulin resistance **(37).** Adipose tissue IL-6 expression accounts for 30% of systemic IL-6, &circulating IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, &insulin resistance **(38).** Plasma IL-6 concentrations predict the development of T2DM **(37).**

Tumor necrosis factor α (TNFα) was the first cytokine to be implicated in the pathogenesis of obesity &insulin resistance **(39),** where macrophages are the its major source in adipose tissue **(40).** Chronic exposure to TNFα induces insulin resistance both in vitro &in vivo **(41**).

Retinol-binding protein 4 (RBP4)was identified as an adipokine whose expression is increased in the adipose tissue of mice & might contribute to insulin resistance by impairing insulin-stimulated glucose uptake in muscles &elevating hepatic glucose production, although the mechanism is not fully clear **(42).**

Omentin rather novelvisceraladipokine, that increases insulin sensitivity in adipocytes. Plasma levels of omentin-1, the major circulating isoform, are inversely correlated with body mass index (BMI), waist circumference, leptin levels, &insulin resistance syndrome & are positively correlated with adiponectin & high-density lipoprotein (HDL) levels.**(43-45).**

3.Other adipocyte factors:

3.a.Cortisol produced by adipose tissue. Elevated glucocorticoid levels cause insulin resistance & T2DM, primarily by opposing the anti-gluconeogenic effects of insulin in the liver**(46).**

There is favoured role of waist circumference in risk stratification.**(47)** as well as in diagnosis of metabolic syndrome.**(48,49).** Visceral adiposity is characteristic of people with an "apple-shaped" fat distribution, who appear to have a greater risk of developing insulin resistance than individuals with more peripheral "pear-shaped" fat distribution **(50).** The "portal theory" suggests that insulin resistance in the liver arises from visceral fat drainage directly into the liver via the portal vein **(51).** The increased delivery of FA & cortisol, as well as adipokines**(52)**, could promote hepatic insulin resistance. Other molecular differences between visceral &peripheral fat may also contribute to insulin resistance associated with visceral adiposity **(53).**

B. Inflammatory mechanisms

Systemic chronic inflammation has been proposed to have an important role in the pathogenesis

of obesity-related insulin resistance **(54,55).** Experimental, epidemiological, &clinical evidence produced during the past decade causally links inflammation to the development of insulin resistance & T2DM**(56). B**iomarkers of inflammation, such as TNFα, IL-6, & C-reactive protein (CRP), are present at increased concentrations in individuals who are insulin resistant &obese, & these biomarkers predict the development of T2DM. Activation of inflammatory pathways in hepatocytes is sufficient to cause both local **(57)** as well as systemic insulin resistance **(58).**

Obesity is characterized by macrophage accumulation in white adipose tissue, enhancing development of adipose tissue inflammation **(40).** Adipose tissue macrophages (ATMs) are likely to contribute to the production of several of the adipokines discussed earlier**.(56).**

C. Neural mechanisms

The brain processes information from adiposity signals such as insulin & leptin, which circulate in proportion to body fat mass, &integrates this input with signals from nutrients such as FAs **(59,60)** then sends in response signals to control feeding behavior &substrate metabolism in ways that promote homeostasis of both energy stores &fuel metabolism. Misalignment of food intake with the expression levels of neuroactive peptides, such as leptin, could create metabolic imbalances that alter insulin sensitivity. **(61)**

Cell-intrinsic mechanisms:

Ectopic fat storage:

Increased circulating FAs & other lipids that occur in obesity lead to ectopic fat storage as triglycerides in muscle &liver (whose accumulation has been implicated in insulin resistance **(62, 63)**

Oxidative stress correlates with fat accumulation & regarded as causative factor in the development of insulin resistance **(64, 65).**

Mitochondrial dysfunction increases as insulin resistance ensues associated with significantly higher levels of triglycerides in ectopic fat accumulation in both muscle &liver especially in the elderly. **(66).**

Endoplasmic reticulum (ER) stress, a strain is imposed by obesity on the ER machinery, triggering an ER stress response that impairs the insulin signaling pathway **(67).**

Quantification of Insulin resistance

Various societies had worked on measurement of insulin resistance as WHO consensus group and the European Group for the Study of Insulin Resistance with no agreed upon single diagnostic value. **(68, 69)**

A metaanalysis for identification of insulin resistant individuals using routine clinical measurements employed multicentric study of 17 European clinical recruitment centers, San Antonio & Texas studies of Pima Indians &Mexican Americans to develop decision rules by the tree nodal models & showed that a value of HOMA-IR =4.67 is indicative for insulin resistance in obese T2DM. **(70).**

The variant methods for measurement of insulin resistance are grouped as follows:

A. Clamp techniques &insulin infusion tests:

"Clamp" techniques measure peripheral insulin sensitivity in vivo via time consuming, &labor intensive, complicated procedures that are impractical in an office setting. **(71)**.

1. Hyperinsulinemic-euglycemic clamp:

The " gold ' standard for evaluating insulin sensitivity, being the most scientifically sound technique against which all other tests are being compared, it requires a steady IV infusion of insulin to be administered in one arm. The serum glucose level is "clamped" at a normal fasting concentration by administering a variable IV glucose infusion in the other arm. Then, numerous blood samplings are taken to monitor serum glucose so that a steady "fasting" level can be maintained. The patient is more insulin resistant when tissues take up less glucose tissues during the procedure.(**71)**

2.Hyperinsulinemic-hyperglycemic clamp:

A variation of Hyperinsulinemic-euglycemic clamp technique, as it provides a better measurement of pancreatic beta cell function but is less physiologic than the euglycemic technique. **(72)**

B.Minimalist approach:

Alternative tests have been developed to overcome the obstacles of the dynamic clamp techniques though correlating reasonably well with them. most of these methods require IV access & multiple venipunctures, making them relatively impractical for office assessment. **(71)**

Insulin sensitivity test (IST):

A defined glucose load is infused intravenously besides a fixed-rate infusion of insulin over approximately 3 hours. Somatostatin is infused simultaneously to prevent insulin secretion, inhibit hepatic gluconeogenesis & delay secretion of counter-regulatory hormones— particularly glucagon, growth hormone, cortisol, &catecholamines. Fewer blood samples are required for this test; the mean plasma glucose concentration over the last 30 minutes of the test reflects insulin sensitivity..**(73)**

1. Insulin tolerance test (ITT):

Measures the decline in serum glucose after an IV bolus of regular insulin (0.1–0.5 U/kg) is administered. Several insulin &glucose levels are sampled over the following 15 minutes.It primarily measures insulin-stimulated uptake of glucose into skeletal muscle.The test is so brief, there is very little

danger of counter-regulatory hormones interfering with its results. **(72)**

3. Continuous infusion of glucose with model assessment (CIGMA):

Requires fewer venipunctures. A constant IV glucose infusion is administered, & samples for glucose & insulin are drawn at 50, 55, & 60 minutes. Then, amathematical model is used to calculate SI. The results are reasonably compatible with clamp techniques. **(72)**

4. Frequently sampled IV glucose tolerance test (FSIVGTT):

Less labor intensive than clamp techniques yet still requires as many as 25 blood samples over a 3-hour period, &a computer-assisted mathematical analysis. Several variations of the FSIVGTT had been published. **(72, 74)**

5. Oral glucose tolerance test (OGTT):

A mainstay in the diagnosis of impaired glucose tolerance (IGT) &diabetes mellitus in pregnant &nonpregnant women, may be used to assess insulin sensitivity as well, OGTT is better suited for assessment of large populations than the other techniques previously outlined as no IV access is needed. It provides information on beta cell secretion &peripheral insulin action, &various mathematical equations have been used to provide an SI value. **(75)**

C. Indirect methods:

Indirect methods Had been advocated for quantification of insulin resistance for epidemiologic &clinical studies,as they are simpler & inexpensive quantitative tools. Based on measuring plasma insulin levels during fasting state (homeostatic), or after glucose stimulus. The insulin-glucose ratio is calculated with different straightforward mathematical formulas, to assess insulin sensitivity &beta cell function. Though their merits, among weaknesses of these models is that they assume the relationship between glucose &insulin is linear when in fact it's parabolic.**(71)**

1. Fasting insulin (I0):

Is an inexpensive assay, does not require any mathematical calculations. Although I0 is less variable than other fasting procedures in normoglycemic patients, clinicians must still interpret results cautiously due to limitations.(**73).**

2.Glucose/insulin ratio (G/I ratio):

The ratio of glucose to insulin is easily calculated, with lower values depicting higher degrees of insulin resistance. The G/I ratio became popular since its first description in 1998 as an accurate index of insulin sensitivity in women with PCOS, with (95%) sensitivity & (84%) specificity compared to a control group, where a G/I ratio of less than 4.5 is indicative of insulin resistance. (**74)3. Homeostatic model assessment (HOMA)**.

HOMA has been widely employed in clinical research to assess insulin sensitivity. Rather than using fasting insulin or a G/I ratio, the product ofthe fasting values of glucose (G0 expressed in mg/dL) &insulin (I0 expressed in μU/mL) is divided by a constant:

$$\frac{I0 \times G0}{405}$$

22.5 replaces 405 if glucose is expressed in S.I. units. Unlike I0 &the G/I ratio, the HOMA calculation compensates for fasting hyperglycemia. A value greater than 2 indicates insulin resistance. HOMA &I0 values increase in the insulin-resistant patient while the G/I ratio decreases. The HOMA value correlates well with clamp techniques &had been frequently used to assess changes in insulin sensitivity after treatment & to study insulin resistance among PCOs patients of differing ethnic origins. **(73, 76)**

4- Mathematical calculations:

4. A. *Quantitative insulin sensitivity check index (QUICKI).*

QUICKI is a simple, widely used index as a research tool rather than a routine clinical test, it can be applied to normoglycemic & hyperglycemic patients. It is derived by calculating the inverse of the sum of logarithmically expressed values of fasting glucose & insulin:

$$\frac{1}{[\log(I0) + \log(G0)]}$$

Many investigators believe that QUICKI is superior to HOMA as a way of determining insulin sensitivity, which is the inverse of insulin resistance although the two values correlate well. A value of less than 0.339 indicates insulin resistance i.e. as SI decreases, QUICKI values increase.**(77)**

4.B. McCauley Score for measuring the Insulin Sensitivity Index.

The ISI is calculated for fat-free body mass by dividing the glucose disposal rate (M - mg/kg/min) by the average plasma insulin concentration over the final 60 minutes of the 120-minute test.

An ISI of < 6.3 M/mU/l defined individuals with insulin resistance.Themethod as developed by authors uses a weighted combination of fasting insulin (I0 - mU/l), fasting triglycerides (TG - mmol/l), &Body Mass Index (BMI - kg/m2) to estimate the insulin senility index (ISI). The authors presented two formulae for estimating ISI;

One uses I0, BMI, &TG, has a specificity of 0.82 &a sensitivity of 0.63 in comparison with the euglycemic insulin clamp technique

$$ISI = \exp[3.29 - 0.25*\ln(I0) - 0.22*\ln(BMI) - 0.28*\ln(TG)]$$

The other uses only I0 & TG (without BMI) has a specificity of 0.84 &a sensitivity of 0.62 compared to euglycemic insulin clamp technique.

ISI = exp[2.63 - 0.28*ln(I0) - 0.31*ln(TG)] (**78**)

D. Practical office investigations:

In clinical practice, workup is basically dependent on presence of comorbid conditions to which insulin resistance is pathophysiologically related as type 2 diabetes, abdominalobesity, or dyslipidemia, cardiovascular events where no single laboratory test is used for screening or diagnosis (**1**)

Laboratorial Workup might include;

1. Plasma glucose level:

1. Glucose intolerance diagnosis and monitoring (FPG, OGTT, random blood sugar).
2. Diabetes mellitus; IGT, IFG.
3. Chronic hyperglycemia; HbA1c **(79, 80)**

2. Lipid profile:

3. Electrolyte levels:

1. Creatinine, calculation of eGFR. **(79)**
2. Urinalysisformicroalbuminuria. **(48, 80)**
3. Random spot collection sample for albumin-to-creatinine ratio (ACR) is a marker of endothelial dysfunction, 24hrs collection of urine is burdensome **(80).**
4. Uric acid levels - Hyperuricemia is often associated with insulin resistance as a component of the metabolic syndrome.**(48)**

4. **Proinflammatory markers:**

1. Homocysteine elevated level is a risk factor for atherosclerosis **(48),** which predicts macrovascular disease as its levels are regulated by insulin.(**1**)
2. Hs –CRP increased levels are indicative of low grade systemic inflammation accompanying T2DM and atherosclerosis (**14**)

5. **Prothrombotic indicators:**

1. PAI -1 elevated level is associated with IR, correlated with obesity, waist-to-hip ratio, HTN, IO levels, FPG levels, elevated TG &LDL-c levels, signifies impaired fibrinolysis, & indicating increased risk of atherosclerosis. **(48, 79, 81)**
2. Fibrinogen level elevated level is a feature of insulin resistance syndrome according to IDF platinum standard definition of metabolic syndrome (**48**), as it regulates tissue blood flow and insulin delivery to interstitium**(82).**

E. Software calculators:

Diabetes Trials unit-The Oxford center for Diabetes, Endocrinology, and Metabolism in 2004, had developed a software application with updated versions released until 2013.

The HOMA Calculator provides a quick and easy method for researchers to obtain estimates of insulin resistance using the HOMA2 model. The program runs on Windows and Macintosh platforms. It is available as a stand-alone or embedded in an Excel spreadsheet to calculate values for many individuals simultaneously. **(83)**

GlycatedAlbumin(GA)

GA is a ketoamine formed via a non-enzymatic glycation reaction of serum albumin &it reflects mean glycemia over two to three weeks, both serum &plasma samples can be used, GA can be analyzed from the same samples as common biological markers **(84).**

Hence, the concentration of GA in serum, with a half-life of 12–19 days, would be an excellent index of recent ambient glycemia as:

- Albumin can be measured in the blood with fewer issues than fructosamine
- GA increases compliance with testing &improve patient care &outcome, by reducing the number of recommended blood glucose tests i.e., reducing the number of times people have to stick themselves from 86% to 56 % in daily self monitoring of blood glucose (SMBG) testing. **(85).**
- GA represents an enormous potential saving in healthcare cost,supporting a solid economic argument regarding a shift away from more expensive glucose testing.**(85)**
- GA may also have an impact on screening &diagnosing prediabetes or people suffering from metabolic syndrome. **(85)**
- GA has a rapid turnover time in plasma of 2–3 weeks with 1 month intervals for testingtheglycation speed of GA is ten times faster than HbA1c, so GA is likely to reflect the variation in blood glucose &postprandial hyperglycemia **(86).**
- GA directly measures the effects of hyperglycemia on the most prevalent plasma protein **(87)** as it better monitors glycemic excursions where levels of GA & GA/HbA1c ratios increase in subjects with poorly controlled diabetes than in subjects with well-controlled diabetes**(88).**
- It can be used for patients with anemia or hemoglobinopathies for whom the clinically measured hemoglobin A1c level may be inaccurate **(84)** as well as in diabetes patients undergoing hemodialysis**.(89, 90).**
- GA better monitors gestational glycemia over 16 weeks, GA decreases more rapidly than A1c as glycemic control improves**(91).**
- GA is not affected by extracellular–intracellular glucose dynamics but directly produced by the glycation process in the plasma. **(92).**

Among factors that can influence GA values;

1. Increased albumin catabolism induced by chronic micro-inflammatory conditions **(93).**

2. Hyper-metabolic states, as nephrotic syndrome, hyperthyroidism, & glucocorticoid treatment, where GA increases in relation to blood glucose.(**94**)

3. Diminished albumin catabolism, including liver cirrhosis &hypothyroidism decreases GA.(**94**)

Patients &Methods

A Cross sectional descriptive study into which Sixty-Two (62) type 2 diabetic on insulin participants were recruited at Suez Canal University hospital, aged between 25-60 years of age of either gender whose albumin and CBC indices were normal. Smokers, patients known to be CLD or DKD patients, individuals on regular on statins, aspirin or metformin were all excluded.

Methods: Participants voluntarily proposed to join the study, they were briefed about the study by the investigator &upon their informed consent, a thorough interview for eliciting personal, socio-demographic, history clues indicative of any exclusion criteria was held, they underwent through examination & anthropometric measurements namely waist circumference (WC) was taken. Cut –off values are gender dependent.

Male	**≥ 94 cm**
Female	**≥ 80 cm**

(48)

They were grouped depending upon HOMA-IR into group with insulin resistance (29 participants) or without insulin resistance (33 participants).

Specimens taken for FPG, PPPG, HbA1c, CBC, serum albumin all were analyzed on same day of withdrawal.centrifused serum samples were gathered in alicots for analyzing;

1. GA using Glycated serum protein assay kit (GSP, Glycated albumin) provided by Diazyme Laboratories, Germany using the automated analyzer Olympus 400.

2. Serum fasting insulinDRG Insulin Eliza Kit, DRG instruments GmBh.

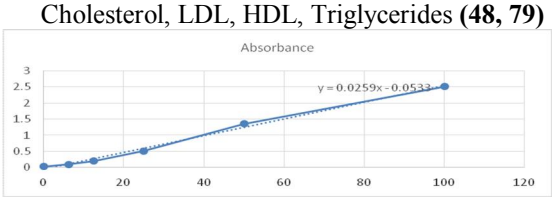
HOMA-IR calculation steps:

1.Average absorbance values for each well were calculated for each set of standards, controls, &patient samples.

2.A standard curve was constructed by plotting the mean absorbance obtained from each standard against its concentration with absorbance value on the vertical (Y) axis&the concentration on the horizontal (X) axis.

3. The equation generated from the standard curve was y= 0.0259 x-0.0533, it was used to calculate the corresponding concentrations for the absorbances revealed by ELIZA procedure.

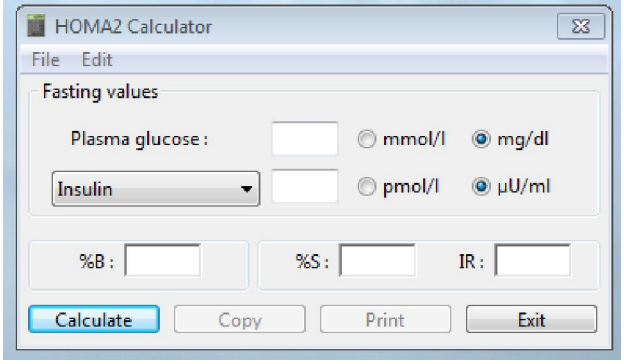
Cholesterol, LDL, HDL, Triglycerides **(48, 79)**



Where Y-axis represents optical density & X-axis represents insulin concentrations).

(Conversion graph of serum insulin optical densities into concentrations with courtesy of Dr. Noha Kamel, lecturer Clinical Pathology, Suez Canal University)

4. The Insulin concentrations were introduced along with fasting plasma glucose in mg/dl per patient into HOMA Calculator v2.2.3 for Windows to reveal HOMA-IR **(83).**



Cut-Off value for HOMA-IR in type 2 diabetes patients 4.67**(70)**

Data analysis:

"IBM SPSS (Version 22) was used for data analysis &presentations. Quantitative data were presented as Mean & Standard Deviation (SD), while qualitative data were presented as frequency &percentage (%).

Differences in means between study groups were tested for statistical significance with independent-samples *t*-test. Chi-square test was used to test the statistical significance of association between categorical variables. Fisher's exact test was used as alternative to Chi-square if >20% of cells had expected values less than 5. Pearson's Correlation was used to evaluate the correlation between every two quantitative variables.

3. Results

Both groups were matched for duration of diabetes, BMI, WC, haemoglobin level,.RBC count, albumin level, FPG & PPPGas there was no statsitically significant difference between them.Age was significantly lower among patients with insulin resistance; while weight, HbA1c &fasting insulin were significantly higher among patients with insulin resistance. GA was insignificantly higher among patients with insulin resistance. (Table 1)

The statistically significant relation between insulin resistance & glycemic control as measured by HbA1c was emphasized; poor control was associated with more insulin resistance & vice versa, though insignificance, the association between Insulin resistance gender, increased waist circumference and BMI was clear (Table 2).

Table 1. Comparing different physical & laboratory parameters between patients with/without insulin resistance

	Insulin Resistance (HOMA-IR)				***p*-value**
	No (*n* = 33)		**Yes** (*n* = 29)		
	Mean	±SD	Mean	±SD	
Age	54.6	7.4	47.8	12.0	**0.008****
Duration of DM	12.6	8.3	10.9	8.0	0.423
Weight (kg)	86.6	15.3	96.1	20.0	**0.040***
BMI (kg/m2)	33.1	8.3	33.9	9.6	0.739
Waist Circum. (cm)	113.2	13.3	115.8	13.7	0.466
FPG	191.5	81.7	235.5	113.6	0.084
PPPG	252.0	130.0	312.3	110.9	0.058
HbA1c	8.5	2.1	10.1	2.4	**0.008****
GA	557.3	167.4	618.1	159.1	0.153
GA/ HbA1C ratio	65.4	9.0	62.4	12.9	0.303
Hb (mg/dl)	12.2	1.0	12.3	1.2	0.747
RCCC (^6)	4.4	0.5	4.6	0.6	0.138
Albumin	3.9	.6	4.1	0.4	0.367
Fasting Insulin	14.0	7.2	38.7	20.3	**<0.001****

*. Statistically significant at p<0.05; Independent Samples *t*test; **. Statistically significant at *p*<0.01; Independent Samples *t*test

Table 2. Relation between Insulin Resistance (HOMA-IR) and Socio-demographic & clinical characteristics

		Insulin Resistance (HOMA-IR)				**Total**	***p*-value**
		No (*n* = 33)		**Yes** (*n* = 29)			
		No.	%	No.	%		
Age	< 50	7	38.89	11	61.11	**18**	0.148[b]
	50 - 60	26	59.1%	18	40.9%	44	
Gender	Male	6	54.55	5	45.45	**11**	0.923[b]
	Female	27	52.9%	24	47.1%	51	
Obesity (BMI)	Non-obese	16	51.6%	15	48.4%	31	0.799[b]
	Obese	17	54.84	14	45.16	**31**	
Obesity [c](Waist circ.)	Non-obese	4	66.67	2	33.33	**6**	0.676[a]
	Obese	29	51.8%	27	48.2%	56	
DM duration	<10	10	47.62	11	52.38	**21**	0.527[b]
	≥10	23	56.1%	18	43.9%	41	
Glycemic control(HA1C)	Good control	10	71.43	4	28.57	**14**	**0.033***[a]
	Fair	6	85.71	1	14.29	**7**	
	Poor	17	41.5%	24	58.5%	41	

*. Statistically significant at p<0.05; [a]. Fisher's Exact test; [b]. Chi-square test,
c. Classification was based on two cut-off points for male (≥94) and female (≥80)

(Table 3) quantifies in terms of Odds Ratio the associations studied in table 2; older patients (50-60 years) had less risk for insulin resistance (58%) compared to younger ones, but not statistically significant. Female patients had 2% greater risk for insulin resistance compared to males with no statistical significance.

Patients with central obesity (waist circumference categorized) had 79% greater risk for insulin resistance than non-obese, with no statistical significance.

Patients with poor glycemic control had 4.33 times greater risk for insulin resistance compared to those with good/fair control, which as statistically significant.

Central obesity was responsible for the significant difference in HbA1c between patients with &without insulin resistance. However, GA was insignificantly higher in obese with insulin resistance compared to patients without insulin resistance, GA/HbA1c ratio didn't differ significantly between patients with & without insulin resistance, either centrally obese or not.(Table 4)

Gender was responsible for the significant difference in HbA1c between female patients with &without insulin resistance and not in males. GA was insignificantly higher in females with insulin resistance compared to females without insulin resistance, even higher than males with insulin resistance. (Table5)

Table 3. Odds ratio for Insulin Resistance &different clinical characteristics

		Insulin Resistance (HOMA-IR)	
		Odds Ratio	**95% confidence Interval**
Age	< 50	1	
	50 – 60	0.42	0.13 – 1.29
Gender	Male	1	
	Female	1.02	0.28 – 3.79
Obesity (BMI)	Non-obese	1	
	Obese	0.94	0.34 – 2.58
Obesity (Waist circ.)	Non-obese	1	
	Obese	1.79	0.30 – 10.61
DM duration	<10	1	
	≥10	0.67	0.23 – 1.94
Glycemic control (HA1C)	Good/ Fair	1	
	Poor	**4.33**	**1.33 – 14.14**

Table 4. Comparing laboratory Markers for glycemic control between patients with/without insulin resistance stratified by abdominal obesity.

	Central Obesity (Waist Circumference for ♂&♀)	**Insulin Resistance** (HOMA-IR)				***p*-value**
		No (*n* = 33)		**Yes** (*n* = 29)		
		Mean	±SD	Mean	±SD	
HbA1c	Non-obese	7.7	2.0	11.0	1.3	0.116
	Obese	8.6	2.1	10.1	2.5	**0.015***
GA	Non-obese	477.7	148.5	686.2	109.2	0.160
	Obese	568.3	169.2	622.1	166.6	0.236
GA/ HbA1C ratio	Non-obese	61.9	9.1	62.5	2.3	0.931
	Obese	65.8	9.0	62.4	13.1	0.251

*. Statistically significant at p<0.05; Independent Samples *t*test

Table 5. Comparing laboratory Markers for glycemic control between patients with/without insulin resistance stratified by gender

	Gender	**Insulin Resistance** (HOMA-IR)				***p*-value**
		No (*n* = 33)		**Yes** (*n* = 29)		
		Mean	SD	Mean	SD	
HbA1c	Male	8.9	3.2	8.8	2.1	0.981
	Female	8.4	1.8	10.5	2.5	**0.001***
GA	Male	621.2	250.0	596.6	100.5	0.842
	Female	543.1	146.0	632.8	173.9	0.051
GA/ HbA1C ratio	Male	69.2	7.1	69.7	16.1	0.944
	Female	64.5	9.3	60.8	11.6	0.218

*. Statistically significant at p<0.05; Independent Samples *t*test

4. Discussion

Serum glycated albumin (GA) is being accepted as an alternative intermediate-term glycation index, though little is known about the physiological &pathological conditions affecting its levels. **(95).**

It's used to fill the gap between self-monitoring of blood glucose (SMBG) which may be rendered cumbersome & expensive & HbA1c which has long turnover &confounders as it could increase compliance, enhance empowerment among diabetes patients &may result in significant health care cost savings.**(85)**.

This Cross sectional study was designed aiming at assessing the correlation of HOMA-IR as quantitative measure of insulin resistance and glycated albumin in comparison to waist circumference in T2DM patients via the hypothesis of negative correlation between central adiposity & glycated albumin.

The current study showed that when participants were classified upon presence or absence of insulin resistance quantified by HOMA-IR, both groups (with & without resistance) where matched for gender, BMI, WC, Hb, RBCs, albumin &duration of diabetes as there was no statically significant difference between the two groups.

However there was a statistically significant relation between insulin resistance & glycemic control; poor control (HbA1C > 8%) was associated with more insulin resistance (HOMA-IR > 4.67) (57.50 % *p* value = 0.039)

This is different from study held by **Notsu*et al.* (2007)** who showed that HbA1c has significant less stringent correlation with HOMA-IR.**(96)**

The current study was concerned with estimating the comparative risk via Odd's ratio between HOMA-IR as a measurable core pathology for obese T2DM & other relevant parameters.

Patients (50-60 years) had less risk for insulin resistance compared with patients (<50 years) as most of participants in both groups were ≥ 50 years old (%59.1 without insulin resistance; 40.9 % with insulin resistance) with no statistically significant difference (*P* value =0.148).

Also females had 2% greater risk for insulin resistance which was statistically insignificant. Obese patients had only 6% lesser risk than non-obese according to BMI classification yet this wasn't statistically significant, while patients with central obesity (greater waist circumference) had 79% greater risk to develop insulin resistance with statistical significance.

Ioannis & Constantine (2009) provided explanations for their results which were similar to the above mentioned results by age-related physiological changes that have marked impact on body composition, inducing a decline in lean (muscle & bone) body mass & total body water in parallel with an increase in fat mass Thus, although excess weight gain may be absent or limited in older adults, the underlying increase of adiposity can be significant. Body weight appears to peak approximately during the 5th or 6th decade of life, with a later peak in women after menopause, & remains rather stable thereafter, whereas a slow weight decline begins after the age of 65 years &continues for the remainder of life. **(97)**

This study also showed that patients with insulin resistance are 4.33 times higher risk to be poorly controlled (HbA1c > 8%). This finding is similar to study held in Turkey where glycatedhaemoglobin was compared to HOMA-IR &it was found that HbA1c levels & HOMA-IR were significantly higher in T2DM than in those with IGT. Also HbA1c-HOMA-IR were higher in IGT participants compared to NGT participants, then NGT group were stratified according to OGTT threshold levels &it was found that the higher glucose levels at 30, 60, 90 minutes the higher the HbA1c &the HOMA-IR. **(98)**

In the current study, Glycemic markers HbA1c, GA, & GA/HbA1c ratio were compared to insulin resistance in obese &non -obese & it was found that HbA1c had a statistically significant (P value = 0.015) higher difference in obese with insulin resistance (10.1% ± 2.5) compared to obese with no insulin resistance (8.6 % ± 2.1)

Though none were statistically significant (*P* value > 0.05), yet the inverse relationship between GA & WC was emphasized as GA was lower in centrally obese with insulin resistance (622.1 µmol/L ± 166.6) than in centrally non -obese with insulin resistance (686.2µmol/L ± 109.2), while the positive relationship between GA & HOMA-IR is evident by the results of higher GA in patients with insulin resistance whether centrally non-obese or non –obese. This might be explained in terms of gender role as GA levels increased among females with insulin resistance (632.8 µmol/L ± 173.9) which is nearly similar to GA levels of centrally obese with insulin resistance mentioned earlier (Table 4), also GA levels in females with no insulin resistance was (543.1 µmol/L ± 146.0) which is coincides with GA levels in obese without insulin resistance, females constituted two thirds of the studied population (51 females vs 11 males as Suez canal university Hospital outpatient Endocrinology & Diabetes clinic visitors are majorly females who are sponsored by ministry of health for healthcare rather than males who are mostly employed & have medical insurance, also few males were eligible to join the study because they were nonsmokers, another reason for recruiting less males into the study is the presence of a comorbidity that might confound the results as cardiovascular events.

The above gender related results are consistent with **Omer *et al.* (2015**) who checked the correlation of type 2 diabetes mellitus with BMI, waist circumference & metabolic profile in Karachi, Pakistan & found that mean BMI & WC in females were high (31.7 ± 5.3 kg/m^2) and (103 ± 12cms) respectively **(99).**

Also cut-off values for insulin resistance diagnosis increase among T2DM obese patients than non-obese patients. This means that in this study, insulin resistance was more likely to occur at higher levels of GA in obese patients.

Another explanation is provided via the presence of inflammatory markers associated with obesity & T2DM **(12,100)** besides the experimental, epidemiological, & clinical evidence that causally links inflammation to the development of insulin resistance & T2DM**(56)** which apparently influence levels of GA.

Conclusion

This study showed that GA levels increase with HOMA-IR levels and female gender and decrease with increased waist circumference.

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