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Original Research Articles

A Decreasing Estimated Glucose Disposal Rate Is Associated with an Increase in Biomarkers of Inflammation

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Abstract: The estimated glucose disposal rate (eGDR) is a validated measure of insulin resistance. Also, it predicts Metabolic Syndrome (MetS), diabetic microvascular and macrovascular complications, atherosclerotic cardiovascular disease (ASCVD) and mortality. However, mechanistic insights examining the relationship between eGDR and the above sequela are scanty. Accordingly, we investigated the relationship between the eGDR and a detailed repertoire of biomarkers of inflammation, oxidative stress, and adipokine dysregulation in a cohort (n = 78) comprising nascent MetS without the confounding of type 2 diabetes mellitus(T2DM), ASCVD, smoking, chronic inflammation, and hypolipidemic drug therapy and matched controls using both tertiles of eGDR and correlations with relevant variables. Cardiometabolic features were significantly different across eGDR tertiles and correlated with eGDR. Receiver operating Characteristic (ROC) curve analysis revealed that eGDR was an excellent predictor of MetS with an area under the curve of 0.89. Also, CRP, IL-6, endotoxin, chemerin, leptin, retinol-binding protein-4 (RBP-4) and monocyte TLR-2 abundance and activity were significantly higher in tertile 1 versus tertile 3 of eGDR and all except RBP-4 correlated with eGDR. Biomarkers of oxidative stress were not significant over tertiles of eGDR. In conclusion, in patients without the confounding of T2DM, ASCVD, smoking, macro-inflammation and lipid therapy, the eGDR is an excellent predictor of MetS. It appears based on our findings that a pro-inflammatory state evidenced collectively by increases in hsCRP, endotoxin, chemerin, leptin, RBP-4, IL-6, TLR-2 abundance and activity, could be advanced as a mediating mechanism explaining the increased risk for diabetic complications and ASCVD.

Keywords: Estimated glucose disposal rate; inflammation; metabolic syndrome; CRP

1. Introduction

Insulin resistance has been advanced as a pivotal pathophysiological mechanism for Metabolic Syndrome (MetS), hypertension, Type 2 diabetes mellitus (T2DM), Dyslipidemia, and Atherosclerotic Cardiovascular Diseases (ASCVD) [1–4]. Although the hyperinsulinemic-euglycemic clamp (HIEC) technique is the gold standard for quantifying insulin resistance, it is expensive, laborious, and not practical for large clinical studies. Therefore, the use of other measures to detect insulin resistance, such as the homeostasis model assessment insulin resistance (HOMA-IR) and triglyceride-glucose (TyG) index, has been studied and validated against the HIEC as reliable surrogates of insulin resistance [5–7]. Williams et al. validated a formula they termed the Estimated Glucose Disposal Rate (eGDR) which comprises glycated hemoglobin (HbA1c), waist-to-hip ratio (WHR) or waist

circumference (WC) and presence of hypertension to assess insulin sensitivity to overcome the problem that patients with type1DM (T1DM) face on insulin therapy [8]. Zabala et al. have validated this formula in male patients with T2DM [9]. Numerous studies have shown that the eGDR is a reliable predictor of MetS, diabetic microvascular and macrovascular complications, ASCVD, and mortality [10–16].

Plausible mechanisms to explain the link between insulin resistance and T2DM, ASCVD, MetS include endothelial dysfunction, increased inflammation, increased oxidative stress, and a pro-thrombotic state [1–3,7]. However, mechanistic insights examining the relationship between eGDR and these mechanisms are scanty.

Accordingly, in the present communication, we investigate the relationship between the eGDR and a detailed repertoire of biomarkers of inflammation, oxidative stress, and adipokine dysregulation in a cohort of nascent MetS without the confounding of T2DM, ASCVD, smoking, chronic inflammation and hypolipidemic drug therapy and matched controls using both tertiles of eGDR and correlations with relevant variables.

2. Patients and Methods

In previous reports, significant findings in this cohort focusing on adipokine dysregulation, inflammation and oxidative stress have been reported [17–20]. MetS participants (n = 46) and controls (n = 32) aged 21–69 years were recruited from Sacramento County, CA, USA, using the criteria of the Adult Treatment Panel III (ATP III) as described previously [21,22]. The 5 MetS risk factors include higher waist circumference, elevated triglycerides, low HDL-cholesterol levels, high blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mm Hg) and high glucose level [21,22]. Participants were defined as having MetS, if they had at least three cardio-metabolic features of MetS. Exclusion criteria for healthy control subjects included current use of any blood pressure medications, elevated triglyceride levels (>200 mg/dL), and having 3 or more of the ATP III criteria. Other important exclusion criteria for all subjects, which were determined by a screening questionnaire, clinical examination and baseline chemistries, included diabetes defined by fasting blood glucose level > 125 mg/dL and or a HbA1c > 6.4%, clinical ASCVD, acute or chronic inflammatory disorders, and history of smoking [19]. Major medication exclusion criteria for subjects with MetS included anti-diabetic medications, anti-coagulants, steroids, oral contraceptive therapy, estrogen replacement therapy, anti-inflammatory drugs, statins, as well as other lipid-lowering agents and angiotensin 2 receptor blockers. Additionally, all participants in the study had a highly sensitive C-reactive protein (CRP) level < 10.0 mg/L and a normal white cell count to exclude macro-inflammation [18,19]. The study was approved by the institutional review board of the University of California, Davis and written informed consent was obtained from all participants.

Fasting blood samples were taken from participants after histories and physical examinations. The details of the different assays have been reported previously [17–20]. Plasma lipids, lipoprotein profiles, glucose and HbA1c were assayed by standard laboratory techniques in the Clinical Pathology Laboratory as described previously. Insulin levels were assayed by ELISA (Linco Biosystems, St. Charles, MO, USA) and the homeostasis model assessment insulin resistance index (HOMA-IR) was calculated from glucose and insulin levels as described previously [18]. Endotoxin levels were quantified using reagents from Lonza (Limulus Amebocyte Lysate, QCL 1000; Walkersville, MD, USA). Levels of oxidized low-density lipoprotein (ox-LDL) and nitrotyrosine were measured in the plasma by a sandwich ELISA using reagents from Mercodia (U.S. branch, Winston-Salem, NC, USA) and Bioxytech (Oxis Research International, Inc., Foster City, CA, USA), respectively. Surface expression of Toll-like receptors (TLR2 and TLR4) on monocytes was analyzed by flow cytometry using BD FACS Array as reported previously [18]. Retinol binding protein 4(RBP-4), Chemerin, adiponectin, resistin and leptin levels were measured using reagents from Linco. Interleukin-1 (IL-1) and IL-6 were measured using a multiplex cytokine/chemokine array (Bioplex, San Jose, CA, USA). Nuclear factor-Kappa-beta (NFkB) activity and cytosolic phospho-P38-mitogen-activated protein (MAP) Kinase activity (P38MAPKinase) were assayed as reported [18,23].

The eGDR was calculated as follows:

eGDR(mg/kg/min) = 21.158 − (0.09 * WC) − (3.407 * HT) − (0.551 * HbA1c) [8–10].

Hypertension was defined as reported or on anti-hypertensive medications: yes is 1 and no is 0. HbA1c was reported as a percent.

Adipose tissue insulin resistance was calculated as the product of FFA and fasting insulin levels as reported previously [24]. The details with respect to the other measures reported have been published previously [17–20].

Statistical Analysis

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis, and significance was defined as a two-sided p-value < 0.05. Results are expressed as median and interquartile range. Trend analysis of

eGDR tertiles in our MetS and control participants was evaluated using the Jonckheere-Terpstra (J-T) test for trend. Combining the control and MetS groups, age-adjusted Spearman rank correlation coefficients were also determined to assess the association between eGDR and relevant variables. Logistic regression models were used to compute the Receiver Operating Characteristic (ROC) Area under the curve (AUC) for assessing the efficacy of eGDR in the prediction of MetS.

3. Results

This report comprised 46 patients with MetS and 32 matched controls.

Patients in tertile 1 had the lowest eGDR (lowest insulin sensitivity or highest insulin resistance) compared to the other tertiles [8–10].

As shown in Table 1, all cardio-metabolic features of the MetS were significantly different across tertiles of eGDR. Age and gender were not significantly different across tertiles. Also, non-HDL-C was not significantly different over tertiles. Both proxies of insulin resistance, HOMA-IR and TyG index, were significantly higher in tertile 1 versus 3. In addition, Adipose tissue insulin resistance (Adipo-IR) was significantly increased across tertiles, with the highest levels in tertile 1.

Table 1. Cardio-Metabolic characteristics over eGDR tertiles.

Variable	Tertile 1 (n = 26)	Tertile 2 (n = 26)	Tertile 3 (n = 26)	*p* Trend *
Female/Male, n (%)	19/7 (73/27)	21/5 (81/19)	24/2 (92/8)	0.08
Control/MetS, n (%)	2/24 (8/92)	8/18 (31/69)	22/4 (85/15)	<0.0001
eGDR(mg/kg/min)	4.4 (3.5–5.1)	7.1 (6.4–7.8)	10.4 (9.7–11.3)	<0.0001
Age (years)	55 (48–62)	51 (45–56)	49 (43–59)	0.05
Waist (cm)	114 (108–123)	98 (94–116)	86 (76–94)	<0.0001
BMI (kg/m^2)	37 (34–39)	34 (30–39)	28 (25–29)	<0.0001
Systolic BP (mmHg)	136 (130–138)	127 (121–135)	118 (105–125)	<0.0001
Diastolic BP (mmHg)	85 (81–91)	79 (76–83)	70 (65–75)	<0.0001
Glucose (mg/dL)	98 (94–102)	97 (88–105)	91 (87–94)	0.006
Total cholesterol (mg/dL)	198 (176–211)	191 (177–214)	195 (163–224)	0.96
HDL-cholesterol (mg/dL)	38 (32–47)	41 (33–50)	52 (43–69)	0.0002
Non-HDL cholesterol (mg/dL)	154 (138–169)	154 (142–159)	140 (112–162)	0.08
Triglycerides (mg/dL)	125 (102–156)	109 (88–152)	69 (56–123)	0.001
HbA1c (%)	5.8 (5.5–6.2)	5.4 (5.2–5.7)	5.5 (5.1–5.6)	0.003
HOMA-IR	2.8 (2.3–5.8)	3.1 (1.6–4.3)	1.5 (0.8–2.8)	0.0002
Adipo-IR (mmol/pmol)	81 (64–129)	36 (29–50)	25 (6–54)	0.005
TyG Index	8.8 (8.5–8.9)	8.6 (8.3–8.8)	8.1 (7.7–8.7)	0.0004

* Jonckheere-Terpstra Test for trend for continuous variables and Cochran-Armitage test for categorical variables. Results are reported as median (25th–75th percentile). Abbreviations: Adipo-IR, adipose tissue insulin resistance; TyG, Triglyceride-Glucose.

We also compared the eGDR with the TyG index in predicting MetS. In the present cohort (n = 78), there was no significant difference in the ROC-AUC of eGDR and TyG index: 0.89 vs. 0.88, respectively, $p = 0.78$. In our large National Health and Nutrition Examination Survey (NHANES) (n = 5380) we previously showed that the TyG index was superior to the HOMA-IR in predicting MetS [25]. Hence, we compared the eGDR with the TyG index in NHANES dataset. ROC-AUC analyses revealed that the eGDR was superior to the TyG index as a discriminant of MetS; ROC-AUC of 0.89 with 95% confidence intervals (CI) of 0.88 to 0.90 compared to 0.86 with CI of 0.85–0.87, $p = 0.0003$ as depicted in Figure 1.

In previous reports, biomarkers of inflammation, oxidative stress, and dysregulation of adipokine biology have been detailed in these patients [17–20]. In the present communication, the focus was on those biomarkers that were significantly abnormal in those published studies focusing on their relationships with increasing tertiles of eGDR.

In Table 2 are shown various biomarkers of oxidative stress, inflammation and adipokines across tertiles of eGDR. High-sensitivity (hs) CRP, the prototypic marker of inflammation, was significantly higher in tertile 1 with the highest insulin resistance. Also chemerin, interleukin (IL)-6, and endotoxin levels were significantly higher in tertile 1 of eGDR.

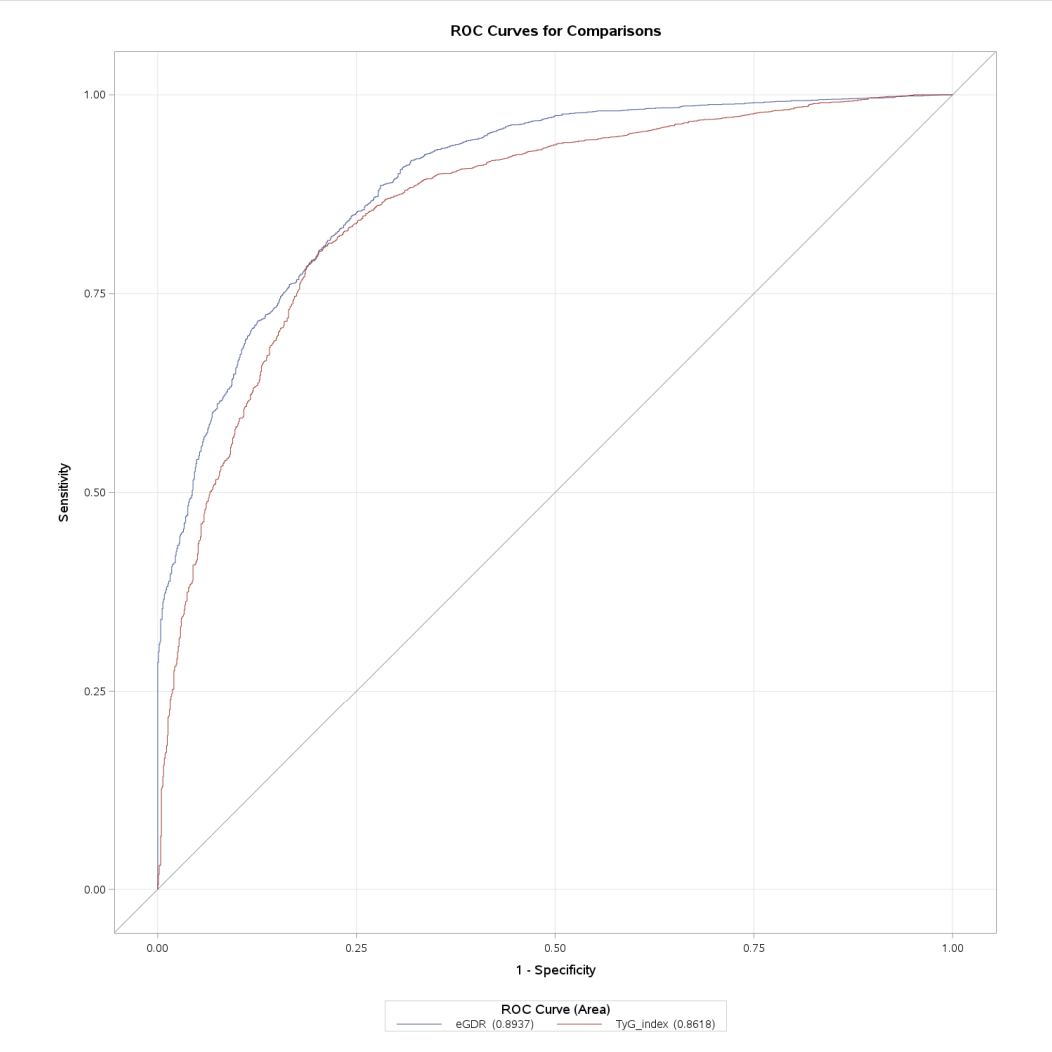

Figure 1. ROC-AUC of eGDR and TyG index in predicting MetS. Delta eGDR − TyG index = 0.03 (95% CI 0.01–0.05), $p = 0.0003$.

Table 2. Biomarkers of inflammation and oxidative Stress over eGDR tertiles.

Variable	Tertile 1 (n = 26)	Tertile 2 (n = 26)	Tertile 3 (n = 26)	*p* Trend *
hsCRP (mg/L)	4.3 (1.7–6.1)	3 (1.3–4.9)	1.2 (0.5–3.1)	0.0003
Resistin (ng/mL)	2.3(1.7–2.6)	2.3(1.5–3.5)	1.9(1.5–2.9)	0.59
Leptin (ng/mL)	83 (57–129)	55 (35–99)	35 (18–46)	<0.0001
Adiponectin (µg/mL)	5.9 (2.7–8.1)	7.2 (4.8–9)	7.5 (3.8–15)	0.12
Chemerin (ng/mL)	383 (370–424)	322 (290–384)	294 (248–336)	0.002
IL1b (pg/mL)	900 (563–1226)	836 (599–912)	839 (421–1056)	0.14
IL6 (pg/mL)	1898 (1696–2179)	1385 (789–1949)	987 (389–1458)	<0.0001
TLR-2 (MFI/10,000 cells)	31 (26–39)	25 (15–32)	21 (16–32)	0.008
TLR-4 (MFI/10,000 cells)	27 (20–32)	26 (22–33)	26 (21–42)	0.71
Endotoxin (EU/mL)	14 (10–15)	9 (4–12)	4 (4–5)	0.009
NFkB activity	0.25 (0.13–0.28)	0.18 (0.05–0.29)	0.05 (0.04–0.07)	0.0001
pp38/p38 MAPKinase activity	0.21 (0.12–0.27)	0.15 (0.08–0.26)	0.08 (0.05–0.09)	0.0003
Nitrotyrosine (nM)	24 (14–156)	21 (9–52)	16 (8–23)	0.11
Ox-LDL (U/L)	42 (34–49)	38 (27–48)	27 (24–43)	0.06
Retinol-binding protein-4(µg/mL)	49 (41–67)	41 (35–49)	38 (34–50)	0.045
NLR	2.0 (1.6–2.3)	2.2 (1.5–2.6)	2.1 (1.6–2.3)	0.80

* Jonckheere-Terpstra Test for trend for continuous. Results are reported as median (25th–75th percentile). Abbreviations: MFI-mean fluorescence intensity; NLR- Neutrophil-Lymphocyte Ratio.

The two important toll-like receptors (TLR) relevant to diabetes and cardiovascular diseases are TLR2 and TLR4 [26]. TLR2 abundance on monocytes was increased from tertile 3 to 1 of eGDR. However, there was no

significant increase in TLR4 abundance on monocytes over tertiles of eGDR. Furthermore, two important cell signaling pathways, nuclear factor -Kappa-beta (NFkB) activity and cytosolic phospho-P38- mitogen activated protein (MAP) Kinase activity (pP38MAPKinase), were also increased in monocytes from tertile 3 to 1 of eGDR.

The neutrophil to lymphocyte ratio (NLR) was not significantly different over tertiles of eGDR in our carefully curated cohort.

For adipokines, Leptin levels were significantly higher in tertile 1 of eGDR as was retinol binding protein 4. However, adiponectin and resistin levels were non-significant over tertiles.

Both biomarkers of oxidative stress, Oxidized-LDL (Ox-LDL) and Nitrotyrosine, were not significantly different over tertiles.

We also undertook correlations to understand relationships with eGDR given the paucity of data with respect to these biomarkers. The eGDR correlated significantly with the TyG index (age-adjusted rho (r) = −0.43, $p < 0.0001$) and HOMA-IR (r = −0.48, $p < 0.0001$). It also correlated with all 5 features of the MetS and adipose tissue insulin resistance (Adipo-IR) following adjustment for age.

Table 3 shows the correlations with biomarkers reported in Table 2. For cardio-metabolic features, the correlations paralleled the tertile analyses.

Table 3. Spearman rank correlations between Egdr and biomarkers of inflammation, oxidative stress and adipokines.

Variable	Rho *	*p*
Age	−0.26	**0.02**
Glucose	−0.32	**0.005**
Systolic BP	−0.64	**<0.0001**
HDL-C	0.42	**0.0001**
Waist circumference	−0.78	**<0.0001**
TG	−0.40	**0.0003**
HbA1c	-0.30	**0.008**
ADIPO-IR	−0.62	**0.0007**
Non-HDL-C	−0.22	0.05
hsCRP	−0.37	**0.001**
Resistin	−0.14	0.45
Leptin	−0.58	**<0.0001**
Adiponectin	0.21	0.13
RBP-4	−0.23	0.09
Chemerin	−0.57	**0.0002**
Interleukin-1beta	−0.12	0.31
Interleukin-6	−0.50	**<0.0001**
Monocyte-Toll-like receptor-2	−0.40	**0.001**
Monocyte-Toll-like receptor-4	−0.04	0.77
Endotoxin	−0.55	**0.003**
Monocyte-NFkB activity	−0.53	**<0.0001**
Monocyte-pP38MAPKinase activity	−0.41	**0.0007**
Nitrotyrosine	−0.26	0.12
Ox-LDL	−0.36	**0.02**
RBP-4	−0.22	0.11
NLR	−0.06	0.60

* Age adjusted Spearman correlation. Abbreviations: NLR, Neutrophil-Lymphocyte Ratio; RBP-4, Retinol binding protein 4.

Furthermore eGDR correlated significantly with hsCRP, IL-6, endotoxin, chemerin, monocyte TLR2 and both monocyte NFkB activity and p-P38MAPKinase activity.

Interestingly OX-LDL levels correlated significantly with eGDR; r = −0.36, $p = 0.02$.

Congruent with the tertile analyses there was no significant correlation between NLR and eGDR; r = −0.06, $p = 0.60$.

4. Discussion

The present investigation was prompted by the lack of data on the relationship between the eGDR and biomarkers of inflammation and oxidative stress to explain the increased risk for MetS, diabetic vascular complications, ASCVD and mortality [11–16]. It captures 3 important cardio-metabolic factors, including adiposity (WC/WHR), glycemia (HbA1c) and hypertension and is a validated measure of insulin resistance based on clamp studies [8,9].

It needs to be emphasized that our study population included controls and patients with nascent MetS without the confounding of T2DM, ASCVD, macro-inflammation, smoking and hypolipidemic drug therapy. Hence we have minimized potential confounders unlike the majority of published studies on the role of eGDR. Further ROC-AUC of 0.89 confirms the eGDR is an excellent discriminant of MetS in the large NHANES data set and is thus a valid surrogate of cardio-metabolic syndromes.

All cardio-metabolic features were significantly different across tertiles of eGDR and correlated significantly with eGDR. Also there were significant differences in validated measures of insulin resistance and its sequala, HOMA-IR and TyG index, over eGDR tertiles and both correlated inversely with eGDR. Furthermore, we make the novel observation that with decreasing tertiles of eGDR there is a significant increase in a measure of adipose tissue insulin resistance, Adipo-IR.

Given the paucity of data on the relationship between oxidative stress and eGDR we reported on 2 important biomarkers in our study. Both Ox-LDL and nitrotyrosine levels were not significant over tertiles of eGDR. Thus our preliminary conclusion is that there is no potential relationship between eGDR and oxidative stress, unlike what we have reported with HOMA-IR and TyG index in this same cohort [27,28]. However, future prospective larger studies can settle the mediating role of oxidative stress in the important complications associated with a decreasing eGDR.

With respect to biomarkers of inflammation, there are some published reports.

In the Finnish Diabetic Study of patients with T1DM (both males and females) with diabetic nephropathy both CRP and IL-6 increased with increasing severity of albuminuria [29]. Also, both correlated inversely with eGDR, a measure of decreased insulin sensitivity or increased insulin resistance. In a subsequent study from Spain the authors reported on insulin resistance define as eGDR below the median in both men and women with T1DM [30]. They studied a large number of biomarkers of inflammation, including CRP, IL-6, leptin, adiponectin and soluble TNF receptors 1 and 2. In men they showed a significant increase in CRP levels only in the insulin-resistant group. In women, none of the biomarkers of inflammation, including CRP were significantly different between insulin-resistant and insulin-sensitive T1DM patients. In men but not women, there was a significant inverse correlation between eGDR and CRP. They clearly did not exclude macro-inflammation (CRP > 10 mg/L) since the upper quartile for CRP in men was 32 mg/L and in women 23.5 mg/L and this could have impacted their results. Finally, in a study from Mexico they reported on a panel of biomarkers of inflammation including resistin, adiponectin, TNF, IL-8, IL-6, IL-10 in T1DM patients with MetS. Only resistin levels were significantly higher in patients with T1DM with MetS [31]. However they did not report on any association between resistin and eGDR.

Based on these 3 studies reporting on eGDR and biomarkers of inflammation in T1DM the data appear confusing with 2 groups reporting a relationship between CRP and eGDR and this could be attributed to the study populations and presence of confounders, etc.

For non-T1DM patients, the data is very scant. In a recent report, Xing et al. reported increase in ASCVD and total mortality in patients with MetS with decreasing eGDR [32]. They also showed that the neutrophil/lymphocyte ratio (NLR) increased with decreasing quartiles of eGDR and claimed it accounted for 8.9% of the total mortality. The study included diabetic patients, smokers and patients with ASCVD and chronic kidney disease. They did not adjust for these confounders. In our carefully curated cohort, we failed to show a significant difference in the NLR over tertiles of eGDR or a correlation with eGDR.

In the China Health and Retirement Longitudinal Study (CHARLS), the authors showed that both eGDR and CRP predicted incident cardiovascular disease (CVD) and both measures combined were at minimum additive [33]. Also mediating analyses revealed a bidirectional relationship with CRP mediating 8.5% of the eGDR-CVD association and eGDR mediating 5.8% of the CRP-CVD association.

In our carefully curated cohort excluding T2DM, smoking, macro-inflammation, lipid-lowering therapy and ASCVD we report on a large repertoire of biomarkers of inflammation and adipokine dysregulation.

In addition to hsCRP, endotoxin, IL-6, chemerin, leptin, RBP-4 levels were significantly increased and correlated significantly with eGDR. Furthermore, monocyte TLR2 and both monocyte NFkB activity and p-P38MAPKinase activity increased with decreasing tertiles of eGDR and also correlated significantly with eGDR.

In summary, the above data on circulating biomarkers (increased hsCRP, endotoxin, IL-6, chemerin, leptin and RBP-4 levels) and cellular mediators (increase in abundance of TLR2 and signal transduction pathways) support a pro-inflammatory state associated with decreasing eGDR i.e., increased insulin resistance. The most common findings in our study that accords with the limited published literature are elevated levels of CRP and IL-6 levels.

In conclusion, in patients without the confounding of T2DM, ASCVD, smoking, macro-inflammation and lipid therapy, the eGDR is an excellent predictor of MetS. Concerning mechanistic insights, it appears based on our findings, a pro-inflammatory state evidenced collectively by increases in hsCRP, endotoxin, chemerin, leptin,

RBP-4, IL-6, TLR-2 abundance and activity could be advanced as mediating mechanisms explaining the increased risk for diabetic microvascular and macrovascular complications and ASCVD. However, given the cross-sectional nature of this preliminary report, it cannot imply cause and effect. This can only be settled with large prospective studies with a wide panel of biomarkers.

Author Contributions

I.J. generated the idea for this publication. B.A.-H. undertook the statistical analyses. Both generated the original version and edited multiple iterations. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

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Informed Consent Statement

All volunteers provided written informed consent.

Data Availability Statement

The data is available from the senior author for review on reasonable request.

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Conflicts of Interest

The authors declare no conflict of interest. Given their editorial roles, Ishwarlal Jialal (Editor-in-Chief) and Beverley Adams-Huet (Editorial Board Member) had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-assisted Technologies

These were not used by the authors submitting this paper.

References

1. Reaven, G.M. Role of insulin resistance in human disease (syndrome X): An expanded definition. *Annu. Rev. Med.* **1993**, *44*, 121–131.
2. DeFronzo, R.A. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: The missing links. The Claude Bernard Lecture 2009. *Diabetologia* **2010**, *53*, 1270–1287. https://doi.org/10.1007/s00125-010-1684-1.
3. Ormazabal, V.; Nair, S.; Elfeky, O.; et al. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc. Diabetol.* **2018**, *17*, 122. https://doi.org/10.1186/s12933-018-0762-4.
4. Caturano, A.; Vetrano, E.; Galiero, R.; et al. Advances in the Insulin-Heart Axis: Current Therapies and Future Directions. *Int. J. Mol. Sci.* **2024**, *25*, 10173. https://doi.org/10.3390/ijms251810173.
5. Wallace, T.M.; Levy, J.C.; Matthews, D.R. Use and abuse of HOMA modeling. *Diabetes Care* **2004**, *27*, 1487–1495. https://doi.org/10.2337/diacare.27.6.1487.
6. Guerrero-Romero, F.; Simental-Mendía, L.E.; González-Ortiz, M.; et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 3347–3351. https://doi.org/10.1210/jc.2010-0288.
7. Gounden, V.; Devaraj, S.; Jialal, I. The role of the triglyceride-glucose index as a biomarker of cardio-metabolic syndromes. *Lipids Health Dis.* **2024**, *23*, 416. https://doi.org/10.1186/s12944-024-02412-6.
8. Williams, K.V.; Erbey, J.R.; Becker, D.; et al. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* **2000**, *49*, 626–632. https://doi.org/10.2337/diabetes.49.4.626.
9. Zabala, A.; Darsalia, V.; Lind, M.; et al. Estimated glucose disposal rate and risk of stroke and mortality in type 2 diabetes: A nationwide cohort study. *Cardiovasc. Diabetol.* **2021**, *20*, 202. https://doi.org/10.1186/s12933-021-01394-4.

10. Epstein, E.J.; Osman, J.L.; Cohen, H.W.; et al. Use of the Estimated glucose disposal rate as a measure of insulin resistance in an urban multiethnic population with type 1 diabetes. *Diabetes Care* **2013**, *36*, 2280–2285. https://doi.org/10.2337/dc12-1693.
11. Chillarón, J.J.; Goday, A.; Flores-Le-Roux, J.A.; et al. Estimated glucose disposal rate in assessment of the metabolic syndrome and microvascular complications in patients with type 1 diabetes. *J. Clin. Endocrinol. Metab.* **2009**, *94*, 3530–3534. https://doi.org/10.1210/jc.2009-0960.
12. Bahrami Hezaveh, E.; Hashemi, R.; Noorafrooz, M.; et al. Estimated Glucose Disposal Rate: A Potential Determinant for Microvascular and Macrovascular Complications in Type 2 Diabetes. *Endocrinol. Diabetes Metab.* **2025**, *8*, e70037. https://doi.org/10.1002/edm2.70037.
13. Nyström, T.; Holzmann, M.J.; Eliasson, B.; et al. Estimated glucose disposal rate and long-term survival in type 2 diabetes after coronary artery bypass grafting. *Heart Vessel.* **2017**, *32*, 269–278. https://doi.org/10.1007/s00380-016-0875-1.
14. Guo, L.; Zhang, J.; An, R.; et al. The role of estimated glucose disposal rate in predicting cardiovascular risk among general and diabetes mellitus population: A systematic review and meta-analysis. *BMC Med.* **2025**, *23*, 234. https://doi.org/10.1186/s12916-025-04064-4.
15. Tao, S.; Yu, L.; Li, J.; et al. Insulin resistance quantified by estimated glucose disposal rate predicts cardiovascular disease incidence: A nationwide prospective cohort study. *Cardiovasc. Diabetol.* **2025**, *24*, 161. https://doi.org/10.1186/s12933-025-02672-1.
16. Chen, X.; Li, A.; Ma, Q. Association of estimated glucose disposal rate with metabolic syndrome prevalence and mortality risks: A population-based study. *Cardiovasc. Diabetol.* **2025**, *24*, 38. https://doi.org/10.1186/s12933-025-02599-7.
17. Bremer, A.A.; Devaraj, S.; Afify, A.; et al. Adipose tissue dysregulation in patients with metabolic syndrome. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E1782–E1788.
18. Jialal, I.; Huet, B.A.; Kaur, H.; et al. Increased toll-like receptor activity in patients with metabolic syndrome. *Diabetes Care* **2012**, *35*, 900–904.
19. Jialal, I.; Devaraj, S.; Adams-Huet, B.; et al. Increased cellular and circulating biomarkers of oxidative stress in nascent metabolic syndrome. *J. Clin. Endocrinol. Metab.* **2012**, *97*, E1844–E1850.
20. Jialal, I.; Devaraj, S.; Kaur, H.; et al. Increased chemerin and decreased omentin-1 in both adipose tissue and plasma in nascent metabolic syndrome. *J. Clin. Endocrinol. Metab.* **2013**, *98*, E514–E517.
21. Grundy, S.M.; Cleeman, J.I.; Daniels, S.R.; et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* **2005**, *112*, 2735–2752.
22. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute: American Heart Association: World Heart Federation; International Atherosclerosis Society; and International Association for the study of Obesity. *Circulation* **2009**, *120*, 1640–1645.
23. Jialal, I.; Adams-Huet, B.; Pahwa, R. Selective increase in monocyte p38 mitogen-activated protein kinase activity in metabolic syndrome. *Diab Vasc. Dis. Res.* **2016**, *13*, 93–96.
24. Adams-Huet, B.; Devaraj, S.; Siegel, D.; et al. Increased adipose tissue insulin resistance in metabolic syndrome: Relationship to circulating adipokines. *Metab. Syndr. Relat. Disord.* **2014**, *12*, 503–508.
25. Adams-Huet, B.; Zubirán, R.; Remaley, A.T.; et al. The triglyceride-glucose index is superior to homeostasis model assessment of insulin resistance in predicting metabolic syndrome in an adult population in the United States. *J. Clin. Lipidol.* **2024**, *18*, e518–e524. https://doi.org/10.1016/j.jacl.2024.04.130.
26. Jialal, I.; Kaur, H.; Devaraj, S. Toll-like receptor status in obesity and metabolic syndrome: A translational perspective. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 39–48.
27. Adams-Huet, B.; Jialal, I. Correlates of Insulin Resistance in Nascent Metabolic Syndrome. *Clin. Med. Insights Endocrinol. Diabetes* **2023**, *16*, 11795514231168279. https://doi.org/10.1177/11795514231168279.
28. Adams-Huet, B.; Jialal, I. An Increasing Triglyceride-Glucose Index Is Associated with a Pro-Inflammatory and Pro-Oxidant Phenotype. *J. Clin. Med.* **2024**, *13*, 3941. https://doi.org/10.3390/jcm13133941.
29. Saraheimo, M.; Teppo, A.M.; Forsblom, C.; et al. Diabetic nephropathy is associated with low-grade inflammation in Type 1 diabetic patients. *Diabetologia.* **2003**, *46*, 1402–1407. https://doi.org/10.1007/s00125-003-1194-5.
30. Llauradó, G.; Gallart, L.; Tirado, R.; et al. Insulin resistance, low-grade inflammation and type 1 diabetes mellitus. *Acta Diabetol.* **2012**, *49*, 33–39. https://doi.org/10.1007/s00592-011-0257-1.
31. Ferreira-Hermosillo, A.; Molina-Ayala, M.; Ramírez-Rentería, C.; et al. Inflammatory Cytokine Profile Associated with Metabolic Syndrome in Adult Patients with Type 1 Diabetes. *J. Diabetes Res.* **2015**, *2015*, 972073. https://doi.org/10.1155/2015/972073.
32. Xing, D.; Xu, J.; Weng, X.; et al. Correlation between estimated glucose disposal rate, insulin resistance, and cardiovascular mortality among individuals with metabolic syndrome: A population-based analysis, evidence from NHANES 1999–2018. *Diabetol. Metab. Syndr.* **2025**, *17*, 11. https://doi.org/10.1186/s13098-024-01574-8.

33. Xu, L.; Ma, J.; Xu, Y. The effects of estimated glucose disposal rate and high sensitivity C-reactive protein on risk of incident cardiovascular diseases in middle-aged and elderly Chinese adults: A nationwide prospective cohort study. *Lipids Health Dis.* **2025**, *24*, 234. https://doi.org/10.1186/s12944-025-02653-z.