Final Report for the Wael Al-Mahmeed & IAS Research Training Grant and Fellowship

Title: Association of Triglyceride-Glucose (TyG) Index with Metabolic Syndrome, Hepatic Fibrosis, and Hepatic Steatosis in Individuals with Severe Obesity

Fellow: Sepideh Salehabadi, Mashhad University of Medical Sciences, Mashhad, Iran

Supervisor: Thozhukat Sathyapalan, Academic Diabetes Endocrinology and Metabolism, Hull York Medical School, University of Hull, UK of Great Britain and Northern Ireland, Hull, UK

Background and Aims:

Obesity has emerged as a major global health concern, with its prevalence steadily increasing over the past few decades. Obesity is associated with numerous metabolic complications, including cardiovascular disease, non-alcoholic fatty liver disease, type 2 diabetes, and dyslipidemia. As a result, effective interventions for obesity management have become crucial in reducing the burden of associated metabolic disorders. Bariatric surgery has gained significant attention as the most effective approach for weight loss and metabolic improvement in individuals with severe obesity. Beyond the primary goal of weight reduction, bariatric surgery has been shown to induce substantial cardiometabolic benefits, including improvements in glucose homeostasis, insulin sensitivity, and lipid profile.

One promising and cost-effective marker that has gained attention in the evaluation of insulin resistance is the Triglyceride-Glucose (TyG) index (defined as fasting triglycerides [mg/dL] x fasting plasma glucose [mg/dL]/2). The TyG index is a simple mathematical formula calculated from the routinely-measured biochemical variables of fasting triglycerides (TG) and fasting plasma glucose (FPG). The TyG index has shown to have a strong correlation with other established indices of metabolic dysfunction, such as the homeostatic model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI).

Given the metabolic benefits observed following bariatric surgery and the potential utility of the TyG index in assessing metabolic health, the impact of bariatric surgery on the TyG index deserves further investigation. Therefore, we conducted a cross sectional study of approximately 1300

patients having a BMI greater than 40 kg/m2 or a BMI between 35-40 kg/m2 and two comorbidities who were referred to an outpatient clinic for metabolic surgery (sleeve gastrectomy (SG) or Roux en-Y gastric bypass (RYGB). All clinical and laboratory findings of patients were recorded at baseline as well as different post-surgery follow-up time-points.

Besides setting up the aforementioned database, our main objectives of studies during the fellowship course were:

1. To explore the association of the TyG index with the severity of hepatic steatosis
2. To explore the association of the TyG index with the severity of hepatic fibrosis
3. To explore the association of the TyG index with metabolic syndrome
4. To explore the ability of the TyG index to identify individuals with NAFLD at risk of liver fibrosis

Results:

A total of 1005 participants were finally enrolled. Clinical and laboratory characteristics, grouped by liver steatosis status (grade 0 and 1: no/low grade steatosis; grade 3 and 4: moderate to severe steatosis), are listed in Table 1. The proportion of women in each group was higher. Participants with moderate to severe steatosis had cardiometabolic risk factors (i.e., higher BMI, fasting blood glucose (FBG), HbA1c, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and lower high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), AST/ALT (AAR), fibrosis-4 (FIB4), NAFLD fibrosis score (NFS), insulin, ferritin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)). Additionally, the TyG index was higher in participants with moderate to severe steatosis.

Table 1. Baseline characteristics of individuals with no/low or moderate/severe **steatosis**			
	no/low grade steatosis	**Moderate to severe steatosis**	**P-Value**
Sex (F/M)	187/18	519/152	<0.001
Age	36.37±11.16	38.39±10.28	0.016
BMI	43.66±6.55	45.53±6.53	<0.001
TG	129.94±72.51	157.22±78.87	<0.001
Chol	180.72±39.63	186.65±39.42	0.065
HDL	45.62±10.11	44.00±10.07	0.049
LDL	107.66±32.63	113.54±32.43	0.026
AST	20.21±7.68	26.42±16.78	<0.001
ALT	21.46±11.33	33.54±25.24	<0.001
GGT	25.14±12.91	33.88±25.11	0.060
ALP	189.67±63.59	200.42±69.68	0.053
AAR	1.05±0.38	0.88±0.33	<0.001
FIB4	0.57±0.29	0.64±0.34	0.013
NFS	-1.66±1.35	-1.22±1.41	<0.001
TYG index	3.74±0.22	3.87±0.23	<0.001
FBG	96.41±16.72	109.11±36.78	<0.001
HBA1C	5.59±0.75	5.97±1.24	<0.001
HOMA-IR	4.49±3.16	6.41±4.49	<0.001
Insulin	18.63±12.01	23.84±14.24	<0.001
Ferritin	57.49±50.72	86.84±87.20	<0.001

Body mass index (BMI), fasting blood glucose (FBG), HbA1c, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and lower high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), AST/ALT (AAR), fibrosis-4 (FIB4), NAFLD fibrosis score (NFS), insulin, ferritin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

As shown in Table 2, participants with liver fibrosis had a positive cardiometabolic risk (i.e., higher BMI, FBG, HbA1c, TG, ALT, AST, AAR, FIB4, NFS, insulin, ferritin, HOMA-IR). Additionally, the TyG index was higher in participants with liver fibrosis.

Table 2. Baseline characteristics of individuals with or without **fibrosis**

	Without liver fibrosis	**With liver fibrosis**	**P-Value**
Sex (F/M)	277/41	145/56	<0.001
Age	37.78±10.43	38.32±10.24	0.564
BMI	44.72±6.67	46.27±6.44	0.009
TG	143.41±71.45	166.51±76.73	0.001
Chol	186.48±38.23	186.46±39.72	0.995
HDL	43.58±9.15	43.17±9.40	0.628
LDL	115.91±32.13	112.93±32.60	0.315
AST	21.62±9.97	26.42±16.78	<0.001
ALT	21.46±11.33	33.54±25.24	<0.001
GGT	25.14±12.91	33.88±25.11	0.060
ALP	189.67±63.59	200.42±69.68	0.053
AAR	1.05±0.38	0.88±0.33	<0.001
FIB4	0.57±0.29	0.64±0.34	0.013
NFS	-1.66±1.35	-1.22±1.41	<0.001
TYG index	3.74±0.22	3.87±0.23	<0.001
FBG	96.41±16.72	109.11±36.78	<0.001
HBA1C	5.59±0.75	5.97±1.24	<0.001
HOMA-IR	4.49±3.16	6.41±4.49	<0.001
Insulin	18.63±12.01	23.84±14.24	<0.001
Ferritin	57.49±50.72	86.84±87.20	<0.001

Body mass index (BMI), fasting blood glucose (FBG), HbA1c, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and lower high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), AST/ALT

(AAR), fibrosis-4 (FIB4), NAFLD fibrosis score (NFS), insulin, ferritin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

As shown in Table 3, participants with metabolic syndrome had a positive cardiometabolic risk (i.e., higher FBG, HbA1c, TG, insulin, HOMA-IR). Additionally, the TyG index was higher in participants with metabolic syndrome.

Table 3. Baseline characteristics of individuals with or without **metabolic syndrome**

	MHO	**MeS**	**P-Value**
Sex (F/M)	277/41	145/56	
Age	36.51±10.03	39.37±10.61	0.033
BMI	44.89±6.89	45.09±6.17	0.802
TG	99.80±26.27	165.54±90.87	<0.001
Chol	188.3±35.05	185.25±39.83	0.541
HDL	55.37±8.45	42.79±8.89	<0.001
LDL	110.31±29.40	112.13±32.74	0.658
AST	23.62±11.33	24.55±15.47	0.628
ALT	29.56±22.72	30.17±22.47	0.831
GGT	26.82±7.77	32.60±25.74	0.550
ALP	196.37±72.86	198.89±70.33	0.779
AAR	1.05±0.38	0.88±0.33	0.224
FIB4	0.65±0.36	0.64±0.33	0.745
NFS	-1.53±1.35	-1.18±1.35	0.053
TYG index	3.63±0.12	3.89±0.23	<0.001
FBG	89.71±6.00	110.99±37.99	<0.001
HBA1C	5.44±0.55	6.04±1.30	<0.001
HOMA-IR	4.03±2.63	6.39±4.64	<0.001
Insulin	18.06±11.52	23.18±14.39	0.006

Ferritin	80.85±92.64	80.71±87.68	0.990

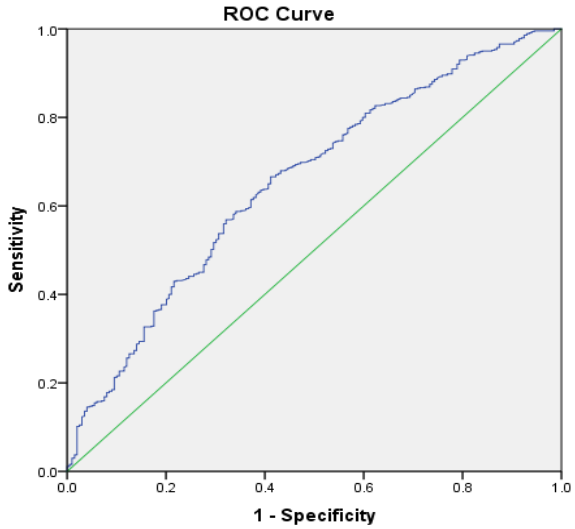
Body mass index (BMI), fasting blood glucose (FBG), HbA1c, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and lower high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), AST/ALT (AAR), fibrosis-4 (FIB4), NAFLD fibrosis score (NFS), insulin, ferritin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

The TyG index as a predictor for liver steatosis and fibrosis

The AUROC value of the TyG index for predicting liver steatosis was 0.655 (0.611–0.698, P < 0.01), and the cutoff value of the TyG index was 3.76, with 64% sensitivity and 60% specificity. That is, the TyG index would be an acceptable predictor of liver steatosis if the value was 3.76 or above (Figure 1A).

The AUROC value of the TyG index for liver fibrosis was (0.652, 95% CI 0.604–0.700) and the cutoff value of the TyG index was 3.74, with 80% sensitivity and 50% specificity. Thus, TYG index can be a good screening tool for liver fibrosis in this group of patients (Figure 1B).

A.



B.

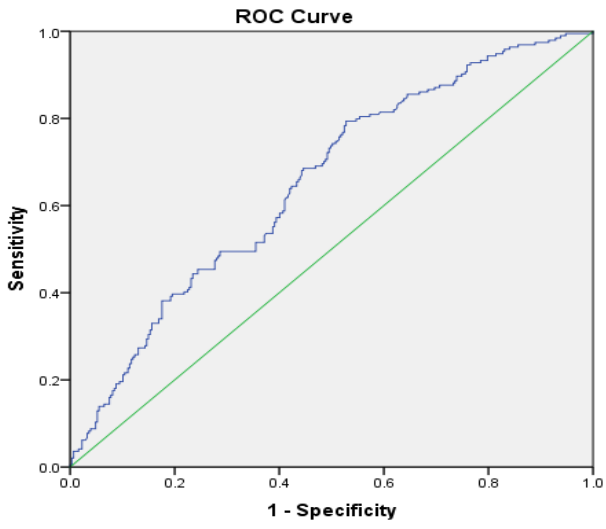


Figure 1. A. Area under the receiver operating characteristics curve (AUROCs) of the TyG index for liver steatosis, B. AUROCs of the TyG index for liver fibrosis

The TyG index as a predictor for metabolic syndrome

The AUROC value of the TyG index for predicting metabolic syndrome was 0.840 (0.805–0.875, $P < 0.01$), and the cutoff value of the TyG index was 3.79, with 64% sensitivity and 92% specificity. That is, the TyG index would be great predictor of metabolic syndrome if the value was 3.79 or above (Figure 2).

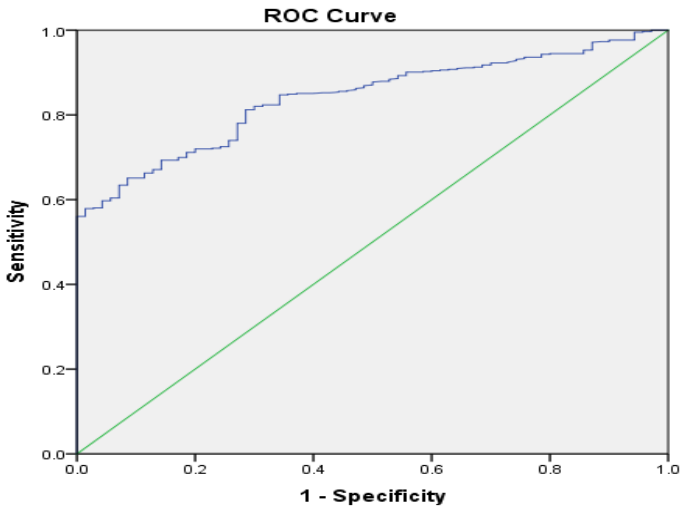


Figure 2. Area under the receiver operating characteristics curve (AUROCs) of the TyG index for metabolic syndrome

The TyG index was associated with fatty liver grade

Participants in the steatosis group were further divided into four fatty liver grade according to the ultrasonography: the without steatosis (0), mild steatosis (1), moderate steatosis (2) and severe steatosis (3) (p-value <0.001) (Figure 3).

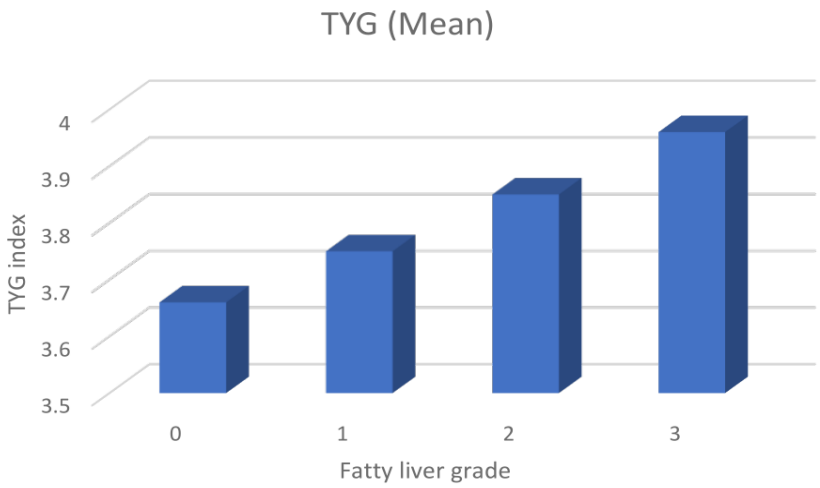


Figure 3. The TyG index in subjects by severity of liver steatosis

Logistic regression analysis of the association of TYG index with liver steatosis

Binary logistic regression was used to explore the association of the TyG index with liver steatosis. The TyG index was associated with liver steatosis upon univariate analysis (OR = 12.680, 95% CI 5.820–27.627, P <0.001).

Logistic regression analysis of the association of TYG index with liver fibrosis

Binary logistic regression was used to explore the association of the TyG index with liver fibrosis. The TyG index was associated with liver fibrosis upon univariate analysis (OR = 9.996, 95% CI

4.349–22.978, P <0.001). Moreover, this relationship remained significant (OR = 6.828, 95% CI 1.056–44.145, P = 0.044), even after adjusting for BMI, sex, age, SBP, DBP, uric acid, HbA1c, ALT, AST, GGT and HDL-C.

Interpretation and Conclusion

The results of this study elucidate the significant associations between the Triglyceride-Glucose (TyG) index and various metabolic conditions in individuals with severe obesity, particularly focusing on metabolic syndrome, hepatic steatosis, and hepatic fibrosis.

Association with Metabolic Syndrome: The TyG index was identified as a strong predictor of metabolic syndrome, with an AUROC value of 0.840. This suggests that the TyG index can effectively identify individuals at risk for metabolic syndrome, making it a valuable tool for early diagnosis and intervention.

Predictive Value for Hepatic Steatosis and Fibrosis: The study demonstrated that the TyG index is also significantly associated with hepatic steatosis and fibrosis. The AUROC values of 0.655 for steatosis and 0.652 for fibrosis indicate that the TyG index can serve as an acceptable screening tool for these liver conditions. The established cutoff values (3.76 for steatosis and 3.74 for fibrosis) further underscore its clinical utility in identifying patients who may require closer monitoring and management.

Cardiometabolic Risk Factors: Participants with higher TyG index values exhibited a positive cardiometabolic risk profile, characterized by elevated BMI, triglycerides, fasting blood glucose, and insulin levels. This correlation highlights the TyG index's potential as a marker for assessing overall metabolic health in this population.

Logistic Regression Analysis: The binary logistic regression analyses reinforced the TyG index's strong association with both liver steatosis and fibrosis. The odds ratios (OR) indicate a substantial risk increase for liver conditions as the TyG index rises, even after adjusting for confounding variables. This suggests that the TyG index is not only a marker but may also reflect underlying

pathophysiological processes associated with metabolic dysfunction.

Clinical Implications: Given its simplicity and cost-effectiveness, the TyG index can be integrated into routine clinical practice to enhance the screening and management of metabolic disorders in individuals with severe obesity. Early identification through the TyG index could facilitate timely interventions, potentially improving patient outcomes.

Future Research Directions: The findings advocate for further studies to validate the TyG index across diverse populations and explore its role in monitoring treatment responses. Longitudinal studies could elucidate the dynamics of the TyG index over time and its potential as a target for therapeutic strategies.

In conclusion, the TyG index emerges as a promising biomarker for assessing metabolic health and liver conditions in severely obese individuals, providing a practical tool for clinicians in managing obesity-related metabolic disorders. Its application could lead to improved patient care through early detection and intervention.