Effects of Supervised Exercise on Gamma-Glutamyl Transferase Levels in Patients with Isolated Impaired Fasting Glucose and Those with Impaired Fasting Glucose Plus Impaired Glucose Tolerance

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Key words
- gamma-glutamyl transferase
- impaired fasting glucose
- impaired glucose tolerance
- exercise
- cardiovascular risk factors

Abstract

Aim: To study the effects of a supervised exercise program on serum gamma-glutamyl transferase (GGT), glycemic control and cardiovascular risk factors in pre-diabetic patients with isolated impaired fasting glucose (IFG) and those with IFG plus impaired glucose tolerance (IGT).

Methods: Out of 60 pre-diabetic patients (30 with isolated IFG and 30 with IFG+IGT) 24 were randomly assigned to the supervised exercise program (1 h twice a week) and 36 only obtained counselling on the risk of diabetes and its prevention. Patients have been followed over a 12-month period.

Results: The main findings were that patients with IFG+IGT had increased GGT levels at baseline (49.2±27.4 U/L) compared to subjects with isolated IFG (28.1±21.9 U/L) ($p<0.01$), and that GGT levels improved only after the supervised exercise intervention within the IFG+IGT subjects (−17.7±19.6 U/L). Similarly, baseline triglyceride levels were also higher in IFG+IGT patients ($p<0.001$) and there was a decrease through exercise intervention in these patients only ($p<0.05$).

Conclusion: GGT is an unspecific marker of oxidative stress and both high plasma glucose and triglycerides levels may produce oxidative stress. Thus, patients with IFG+IGT seem to have higher levels of oxidative stress than those with isolated IFG. Based on the known association between GGT levels and cardiovascular risk factors, IFG+IGT patients may be at higher risk for the development of cardiovascular diseases. The specific effect of regular exercise on GGT in pre-diabetic patients may contribute to the understanding of the preventive effects related to exercise.

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Introduction

Large prospective cohort studies identified serum gamma-glutamyl transferase (GGT) as a predictor of incident type 2 diabetes [1–4] and recent studies highlight the association between GGT levels and cardiovascular risk factors [5,6]. However, the independent association between serum GGT and pre-diabetes is moderate and its value for the routine risk assessment remains questionable [7,8]. The magnitude of association may depend on the test used for the determination of pre-diabetes. Both the fasting plasma glucose (FPG) levels and the oral glucose tolerance tests (OGTT) are considered as gold standards for the detection of pre-diabetes [9–11]. However, risk factor profiles seem to be different in pre-diabetic subjects with isolated impaired fasting glucose (IFG) and those with impaired glucose tolerance (IGT) or IFG+IGT [9,10,12]. In contrast to isolated IFG, IGT is rather related to risk factors for cardiovascular disease, e.g. features of the metabolic syndrome [12,13]. Oxidative stress may represent one potential common pathophysiological mechanism for the development of type 2 diabetes and cardiovascular complications in those patients [14,15].

Type 2 diabetes is typically a consequence of obesity resulting from sedentary lifestyle and hypercaloric nutrition [16]. Due to hypercaloric nutrition the endoplasmatic reticulum of adipocytes cannot adequately process the excess nutrients resulting in efflux of free fatty acids into the circulation [17]. As a consequence an accumulation of fat occurs in liver and skeletal muscle and the lipotoxicity induces mitochondrial dysfunction and oxidative stress [18]. The related production of reactive oxygen species and inflammatory cytokines are considered as the main mediators of insulin resistance [17]. On the other hand regular endurance training may reduce fat accumulation and improve mitochon-

drial function, antioxidative defense and insulin action in insulin resistant skeletal muscle [19,20]. In addition, increasing evidence suggests a close association between oxidative stress markers, e.g. F2-isoprostanes which are oxidative damage products of arachidonic acids, and GGT levels [21]. Thus, elevated GGT levels may represent an early marker of oxidative stress and sub-clinical inflammation associated with a higher metabolic and cardiovascular risk [21,22]. Taken together, increased GGT levels in pre-diabetic patients may indicate oxidative stress and related insulin resistance which might be improved by regular physical activity.

We hypothesized (1) GGT levels to be higher in patients with IFG+IGT compared to those with isolated IFG and (2) that increasing physical activity should help to reduce oxidative stress and GGT levels especially in patients with IFG+IGT.

Methods

Study participants

These analyses are part of our diabetes prevention study [23,24]. Subjects with IFG, IGT and IFG+IGT were recruited by family physicians in the western parts of Austria, primarily through member screening for high-risk groups, such as first-degree relatives of patients with type 2 diabetes and overweight individuals (BMI >25 kg/m^2) aged between 40 and 65 years. IFG has been defined as a fasting plasma glucose concentration of 100–125 mg/dL and IGT as a plasma glucose concentration of 140–199 mg/dL after 2 h of a 75 g glucose load [25]. Exclusion criteria were the diagnosis of diabetes mellitus, any indication of alcohol abuse, the presence of chronic disease rendering a 3-year survival unlikely, and cardiopulmonary or musculoskeletal diseases not compatible with the planned exercise program. Each subject gave informed consent and the study protocol has been approved by the Ethics Committee of the Medical University of Innsbruck. Out of eligible 72 patients, 38 had isolated IFG and 30 had IFG+IGT, and 4 had isolated IGT. For analyses of exercise effects in IFG and IFG+IGT patients those with isolated IGT had been excluded and 30 patients with isolated IFG were matched for age and gender to the 30 patients with IFG+IGT. Based on initial randomization, 12 subjects (4 males and 8 females) with IFG and 12 (4 males and 8 females) with IFG+IGT constituted the exercise group (EG). 18 subjects with IFG (9 males and 9 females) and 18 with IFG+IGT (9 males and 9 females) constituted the control group (CG). Baseline characteristics of the IFG and IFG+IGT patients of the EG and CG are shown in **Table 1**.

Intervention program

All participants were informed about their risk for developing type 2 diabetes and the associated health problems by their family physicians. They were instructed about the preventive effectiveness of changing their lifestyle, especially losing weight and performing regular physical activity by health promotion and exercise physiology specialists (qualified by Austrian Universities).

For the EG, progressive, individually tailored aerobic exercise programs and circuit-type resistance-training sessions for 1 h twice a week were offered additionally. Aerobic work was performed at intensities below the individual anaerobic threshold (controlled by heart rate monitoring and the rating of perceived exertion) interspersed with short periods of higher intensities. Aerobic exercises employed large muscle groups in activities that are rhythmic, dynamic and aerobic in nature, e.g. walking, running, dancing, skating, swimming, and cross-country skiing. In most of the sessions 6–8 strength training exercises, with 8–12 repetitions per exercise were incorporated. Experienced sport scientists were responsible for the exercise programs. The training sessions took place in well equipped gyms or adequate outdoor places. Patients were followed over a 12-month period.

Measurements

All measurements have been performed before and after the intervention program by the family physicians and exercise physiologists at similar time of day.

a. Anthropometry

Anthropometric measurements were recorded by a standardized protocol. Height and weight were determined using proper calibrated devices.

b. Exercise testing

All exercise tests were assessed on a cycle ergometer (Ergoline 900, Schiller, Switzerland). After measuring heart rate and blood pressure at rest, tests began at a work load of 25 watts and which was increased by 25 watts every 2 min until exhaustion. This protocol has been used with the intention to reach exhaustion between 8 and 12 min of exercise [26]. The pedalling rate had to be held at 70–80 rpm. The test was stopped when the pedalling rate dropped below 40 rpm. Heart rate was continuously monitored with the ECG recording, blood pressure and blood lactate concentration (Biosen 5040, Germany) were measured at the end of each work load. Exercise capacity was expressed in power output (watt).

c. Laboratory assessments

FPG and 2-h post load plasma glucose, HbA1c values, levels of total serum cholesterol and of high-density lipoprotein cholesterol, plasma triglyceride and GGT levels have been determined. Venous blood samples were taken by the family physicians in the early morning hours after overnight fasting and were analysed in accredited laboratories. LDL values were calculated using the Friedewald equation. For conversion from mg/dL to mmol/L divide by 18.02 for glucose concentration, by 38.67 for cholesterol concentrations, and by 88.57 for triglyceride concentration.

We did not define reference values for GGT and did not use any cut-off because GGT levels even in the normal range have been shown to be indicative for insulin resistance [27].

Statistical analysis

Data are presented as means ± standard deviation (SD) or 95 % confidence intervals (CI) or frequencies. Student's t-test was used to compare means of continuous data, the Mann-Whitney U-test was applied to evaluate differences between ordinal or not normally distributed data, and Chi-squared test for analysis of frequencies. Analysis of Variance (ANOVA) for repeated measurements with 2 between-subject factors (EG vs. CG, IFG vs. IFG+IGT) and one within subject factor (measurement time before vs. after intervention) was performed. GGT values were log-transformed for inclusion into the ANOVA model to fulfil the normality assumption. Statistical power (a-posteriori) was >80 % for all differences of GGT and triglyceride levels between groups. P–values <0.05 were considered to indicate statistical significance.

Characteristics	Exercise Group		Control Group	
	IFG	IFG+IGT	IFG	IFG+IGT
	N=12	N=12	N=18	N=18
age (years)	57.8 (6.5)	54.0 (8.0)	57.8 (7.9)	57.6 (5.8)
gender (males/females)	4/8	4/8	9/9	9/9
smokers (yes/no)	2/10	1/11	3/15	2/16
medication (yes/no)				
antihypertensive drugs	7/5	6/6	10/8	9/9
statins	3/9	3/9	4/14	4/14
antidepressants	2/10	2/10	2/16	3/15
thyroid hormones	1/11	2/10	3/15	2/16
stature (cm)	168.7 (9.3)	168.0 (7.8)	170.0 (7.1)	170.3 (9.8)
body mass (kg)	86.9 (14.3)	85.3 (12.0)	80.3 (12.5)	86.8 (8.0)
body mass index (kg/m^2)	30.8 (6.4)	30.2 (3.6)	28.3 (2.8)	30.1 (3.2)
fasting plasma glucose (mg/dL)	111.3 (8.1)	108.9 (9.2)	109.2 (5.9)	108.6 (8.1)
2-h plasma glucose (mg/dL)	117.8 (11.9)	169.7 (22.4)*	105.1 (22.4)	165.8 (15.7)*
HbA1c (%)	5.8 (0.49)	6.2 (0.75)	5.6 (0.43)	5.9 (0.68)
total cholesterol (mg/dL)	229.5 (54.0)	220.3 (31.6)	214.3 (53.2)	214.2 (38.2)
HDL (mg/dL)	62.3 (18.6)	50.8 (10.8)	61.6 (16.9)	52.7 (11.5)
LDL (mg/dL)	142.6 (42.7)	142.1 (30.0)	130.7 (46.6)	134.8 (32.9)
triglycerids (mg/dL)	136.4 (39.8)	181.3 (32.0)*	124.6 (38.1)	165.4 (46.1)*
gamma glutamyltransferase (U/L)	23.9 (25.9)	51.3 (27.6)*	30.9 (19.0)	47.9 (27.9)*
resting heart rate (beats/min)	82.0 (14.4)	81.1 (11.7)	80.4 (14.2)	77.1 (14.5)
resting blood pressure				
systolic (mmHg)	125.8 (21.0)	130.8 (6.7)	128.3 (21.1)	134.0 (14.9)
diastolic (mmHg)	88.8 (8.2)	85.6 (10.3)	84.3 (13.5)	89.3 (14.3)
absolute Pmax (watt)	138.5 (28.3)	129.2 (29.8)	129.8 (31.9)	127.6 (44.4)
relative Pmax (watt/kg)	1.66 (0.51)	1.54 (0.42)	1.64 (0.29)	1.46 (0.48)

Data are means (SD) or frequencies

There are no significant differences between the exercise and control group

*means different mean values between the subgroups (IFG and IFG+IGT) within the exercise or control group ($p<0.05$)

Table 1 Baseline characteristics of patients with impaired fasting glucose (IFG) and impaired fasting glucose+impaired glucose tolerance (IFG+IGT) of the exercise and control group.

Results

Baseline characteristics of IFG and IFG+IGT patients of the EG and the CG are shown in **Table 1**. As indicated by BMI and use of medication most participants suffered from components of the metabolic syndrome. There are no significant differences in baseline values between the EG and the CG. However, levels of the 2-h post load plasma glucose, plasma triglycerides, and plasma GGT were higher in the IFG+IGT subgroups compared to the IFG subgroups of the EG and the CG as well.

The adherence to supervised exercise within the EG was high. Subjects participated in the exercise program on average for 1.8 (0.3) hours per week. Data on additional self-chosen physical activity are incomplete but such activities have been rarely performed and seem not to differ between the EG and CG. Repeated measures ANOVA revealed significant effects between IFG and IFG+IGT for levels of GGT, triglycerides, FPG, 2-h post load plasma glucose, and HDL. GGT levels were on average across measurements significantly higher in patients with IFG+IGT ($p<0.001$). In addition, there was a significant decrease through the exercise intervention in IFG+IGT patients only (p for interaction=0.003). GGT decreased from 51.3 to 33.7 U/L in the EG whereas there was an increase from 47.8 to 54.9 U/L in the CG (**Fig. 1**). Baseline triglyceride levels were also higher in IFG+IGT patients ($p<0.001$) and there was a decrease through exercise intervention in IFG+IGT patients only (p for interaction=0.02) (**Fig. 2**). FPG decreased in all groups from baseline to the second measurement ($p<0.001$). Decrease was stronger in IFG patients (−10.6 vs. −3.8 mg/dL; p for interaction=0.049); however, there was no significant effect of exercise intervention. 2-h post load plasma glucose decreased from baseline to second measurement in IFG+IGT patients (−36.6 mg/dL; p for interaction=0.001). High-density lipoprotein values were lower in IFG+IGT compared to IFG patients ($p=0.02$). Significant within-subject effects were observed for absolute and relative Pmax which both improved only within the EG by the intervention. Absolute Pmax increased by 12.1 (9.2) watt within the EG and by 1.2 (16.8) watt within the CG ($p<0.05$). Sub-analyses revealed that neither gender nor smoking habits nor medication was responsible for the observed differences between groups. No significant between- or within-subject effects were found with regard to body mass, BMI, total cholesterol, LDL, HbA1c, resting heart rate and blood pressure values.

Discussion

The presented findings are consistent with our study hypotheses. First, subjects with IFG+IGT had increased GGT levels compared to subjects with isolated IFG and second, GGT levels have improved only after the supervised exercise intervention within the IFG+IGT group.

Recently, Bianchi et al. [28] demonstrated GGT levels to be independent predictors of IFG+IGT. Oxidative stress may be considered at least one important link between GGT and IFG+IGT. GGT represents an unspecific marker of oxidative stress [1,22] and even mild alterations in glucose metabolism like IFG and IGT may generate oxidative stress and progression of hyperglycaemia [29]. Oxidative stress is associated with insulin resistance which seems to be more pronounced in IFG+IGT than isolated

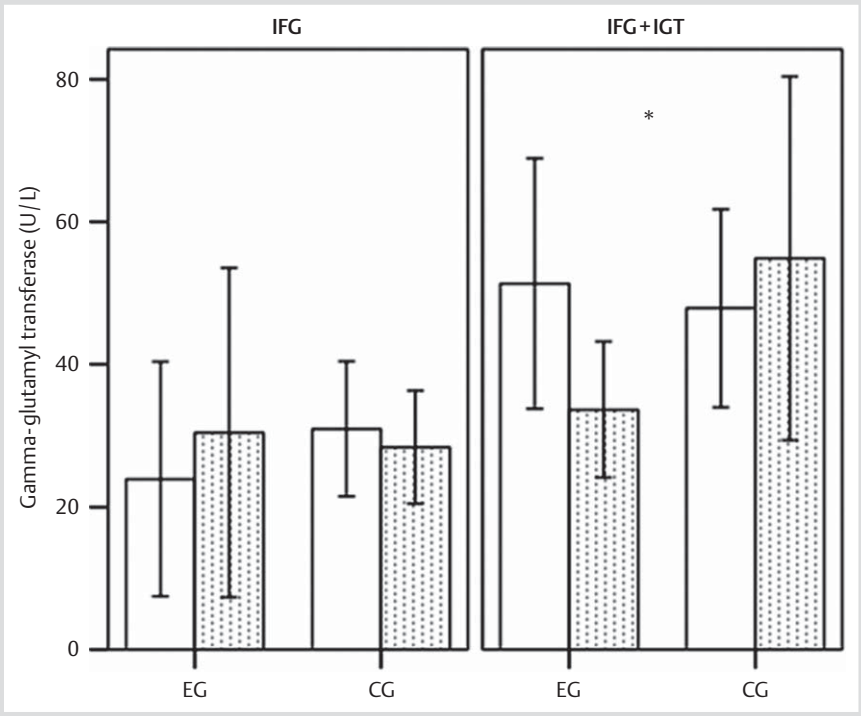

Fig. 1 Changes of gamma-glutamyl tranferase levels from pre- (blank bars) to post- (pointed bars) intervention in patients with impaired fasting glucose (IFG) and impaired fasting glucose + impaired glucose tolerance (IFG + IGT) of the exercise (EG) and the control group (CG). * indicates a significant decrease from pre to post through the exercise intervention within patients with IFG + IGT ($p < 0.05$).

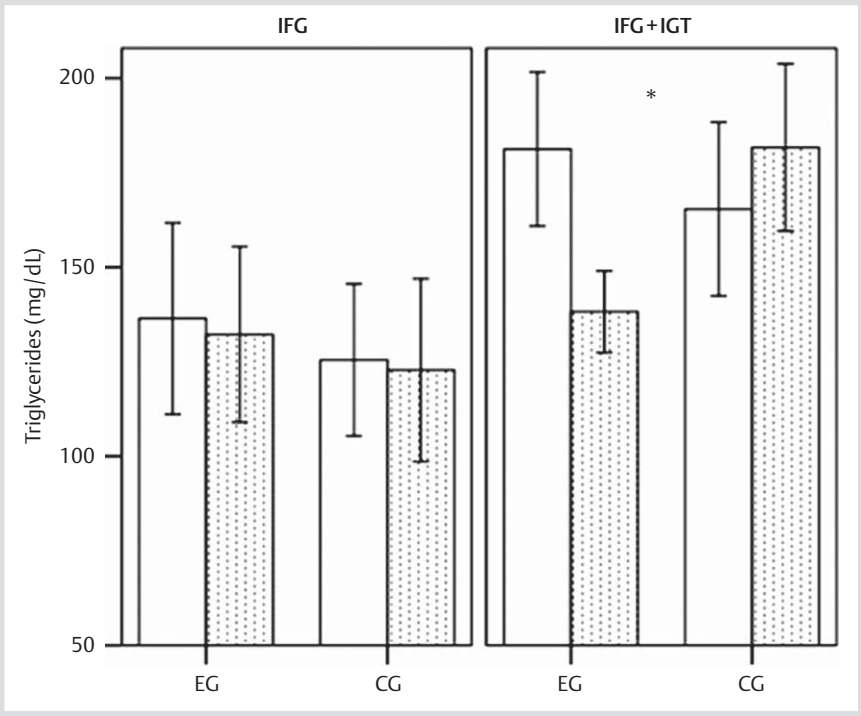

Fig. 2 Changes of triglyceride levels from pre- (blank bars) to post- (pointed bars) intervention in patients with impaired fasting glucose (IFG) and impaired fasting glucose + impaired glucose tolerance (IFG + IGT) of the exercise (EG) and the control group (CG). * indicates a significant decrease from pre to post through the exercise intervention within patients with IFG + IGT ($p < 0.05$).

IFG [30,31]. Insulin resistance occurs in multiple organs and interventions improving insulin resistance are organ dependent, e.g. physical activity primarily improves muscle insulin resistance [32]. However, the increased capacity of glucose disposal by the skeletal muscles should also reduce the accumulation of fat in the liver, improve mitochondrial function and reduce oxidative stress and GGT levels [18]. Thus, our results support the assumption by Nathan et al. (2007) who suggested that patients with isolated IFG suffer rather from hepatic insulin resistance and normal muscle insulin sensitivity whereas those with IFG + IGT manifest both muscle and hepatic insulin resistance [33]. In addition, elevated triglyceride levels have been shown to be positively related to oxidative stress [34] and negatively to insulin sensitivity [35] and were also higher in IGT than IFG [36]. Hypertriglyceridemia may be an important source of oxidative stress. For instance, hypertriglyceridemia has been reported to stimulate leukocytes to produce superoxide anion radicals [37] which in turn might increase GGT levels as observed within the IFG + IGT group of the present study. Reduced mitochondrial content as often observed in these individuals reduces the mitochondrial fatty acid oxidation capacity [38]. This in turn promotes accumulation of fatty acid metabolites and contributes to the development of muscle insulin resistance by activation of protein kinase θ [39]. Aerobic exercise however, protects against lipid accumulation by increas-

ing lipid oxidation capacity [40] and possibly preventing development of muscle insulin resistance.

This is also supported by the observation that lowering triglyceride levels in the IFG + IGT group by the exercise intervention was accompanied by a reduction of plasma GGT concentration. In general, triglyceride levels are indirect measures of insulin sensitivity [35] and lowering triglyceride concentration by regular physical activity reflects improved insulin sensitivity. Surprising the observation that triglyceride and GGT levels were specifically improved within IFG + IGT patients by exercise intervention whereas FPG and 2-h post load plasma glucose improved over time irrespective of the type of intervention. These results may be interpreted in the way that both interventions, exercise and counselling alone, were sufficient to improve isolated IFG and IFG + IGT but exercise was essential to lower plasma triglycerides and related GGT concentrations. Beneficial effects of exercise on triglycerides and GGT have repeatedly been reported [41–43]. It might be speculated that exercise per se resulted in reduced triglyceride levels and the related oxidative stress and its marker GGT. In fact, aerobic exercise was found to reduce postprandial triglyceride levels [44,45]. In addition, physical activity may improve the resistance to oxidative stress and thus support the reduction of GGT concentration. Whereas an acute bout of exercise in untrained subjects usually increases oxidative stress [46] adaptations to chronic exercise result in higher antioxidant capacity and resistance to oxidative stress [20,47]. During the last years, GGT has turned out to be an important cardiovascular risk biomarker. For example, GGT action is related to LDL oxidation [48] and conversely, lowering GGT levels by physical activity should support the protection of LDL oxidation and the related formation of inflammatory atheroma within the vascular endothelial wall [49]. Thus, physical activity may contribute to its evidence based beneficial effects on cardiovascular risk factors and mortality by several mechanisms, including the lowering of elevated GGT concentrations. Taken together our findings highlight the importance of regular physical activity in pre-diabetic patients with combined IFG and IGT.

Limitations

Although potential alcohol abuse and related liver dysfunction cannot be entirely excluded we do not have any indication that this would have been the case. Non-alcoholic fatty liver disease (NAFLD) is relatively common in the normal population (up to 30% in developed countries) and increases in pre-diabetic and diabetic patients dramatically [50]. Thus, we did not assess NAFLD, also because of the fact that changes from pre to post would not have been detected reliably by ultrasonography.

Data on the self-chosen physical activity are incomplete and such activities may have contributed to the observed effects. However, available data suggest no differences between the EG and the CG. Thus, observed effects are very likely resulting from the supervised exercise program.

Conclusions

The presented findings demonstrate elevated GGT levels in pre-diabetic patients with combined IFG + IGT. Whereas glycemic control has improved irrespective of the type of intervention, physical activity was essential to reduce triglyceride and GGT levels in patients with combined IFG + IGT. Due to the well known association between GGT and cardiovascular disease the prescription of regular physical activity seems to be of utmost importance especially for patients with IFG + IGT.

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Conflict of Interest: None.

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