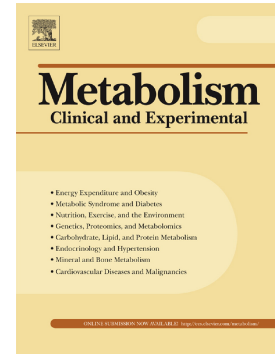


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Lifestyle intervention is more effective in high 1-hour post-load glucose than in prediabetes for restoring β -cell function, reducing ectopic fat, and preventing type 2 diabetes

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Keywords: Prediabetes, Type 2 Diabetes, MASLD, hepatic fat content, ectopic fat, β -cell function, insulin resistance

Highlights:

We compared the effectiveness of a structured lifestyle intervention (LI) in people with normal glucose regulation (NGR) to isolated high 1h-PG and with impaired glucose regulation (IGR, impaired glucose tolerance, impaired fasting glucose or both).

We show that high 1h-PG is an intermediate condition between NGR and IGR in terms of insulin resistance, β -cell function and ectopic fat accumulation, including liver fat content and visceral fat volume.

LI in high 1h-PG is more effective to reduce incident T2D than in IGR, mediated by the restoration of insulin sensitivity and β -cell function toward normal ranges, as well as liver fat content and visceral adipose tissue mass.

1h-PG represents a clinically actionable biomarker that identifies a critical window of opportunity to reverse insulin resistance and impaired β -cell function, key predictors of future complications.

Abstract

Background

High 1-hour-post-load plasma glucose (1h-PG) is an early diabetes risk marker. We hypothesized that isolated high 1h-PG represents an intermediate state between normal glucose regulation (NGR) and impaired glucose regulation (IGR) and is amendable to greater lifestyle intervention (LI) benefit.

Methods

In the Tübingen Lifestyle Intervention Program, 317 people with either NGR, IGR or isolated high 1h-PG without IGR underwent LI for 9 months to achieve $\geq 5\%$ weight loss.

Results

Before LI initiation, insulin sensitivity and β -cell function declined progressively from NGR (n=106) to high 1h-PG (n=96) and to IGR (n=115). Visceral adipose tissue (VAT) volume and liver fat content increased from NGT to high 1h-PG and to IGR. LI improved insulin sensitivity and β -cell function in the high 1h-PG group to levels observed in NGR together with a marked reduction in hepatic fat content. Compared to the IGR group, T2D risk was reduced by 80% (37-96%, $p=0.005$) in the high 1h-PG group during a 12-year follow-up period. The odds of remission to complete normoglycemia were doubled in the high 1h-PG group compared to the IGR group (2.18 [1.13-4.28], $p=0.021$).

Conclusion

High 1h-PG indicates an intermediate metabolic state with pathophysiological changes more severe than in NGR but milder than in IGR. In people with high 1h-PG, LI significantly improved insulin sensitivity and β -cell function and reduced ectopic lipid deposition and the risk of developing T2D compared to IGR. These findings highlight the value of 1h-PG as a clinically useful biomarker, providing a critical window for early intervention to reverse core metabolic defects driving prediabetes and T2D.

1. Introduction

Prediabetes is associated with an increased risk for most conditions projected to be leading causes of disability and death in the coming decades including cardiometabolic, renal and neoplastic disease [1,2]. Current guidelines recommend lifestyle intervention (LI) to prevent progression to type 2 diabetes in people with prediabetes [3]. Recommended multimodal LI is targeted at >5-7% body weight loss via increased physical activity and diet modification. These interventions are cost-effective, and their protective effects are long-lasting [4-6], but the percentage of non-responders likely to progress to type 2 diabetes or develop complications of prediabetes, is high. As younger people participating in LI are more likely to achieve favorable outcomes [7,8], it has been speculated that LI initiated early after the onset of dysglycemia would be beneficial. Thus, different risk assessments to screen people eligible for LI have been proposed.

The International Diabetes Federation (IDF) has proposed the one hour plasma glucose (1h-PG) ≥ 155 mg/dL (8.6 mmol/L) level obtained during a 75-gram oral glucose tolerance test (OGTT) to improve sensitivity of predicting progression to type 2 diabetes compared to current diagnostic criteria [9]. Employing ADA criteria [3] results in diagnosing prediabetes (fasting PG ≥ 100 mg/dL [5.6 mmol/L] and < 126 mg/dL [7.0 mmol/L] or 2-h PG ≥ 140 mg/dL [7.8 mmol/L] and < 200 mg/dL [11.1 mmol/L]) in 41.1 % of people that do not progress to type 2 diabetes within 10 years, while after 10 years, 20 % of people with type 2 diabetes were not diagnosed with prediabetes at baseline that would have prompted LI [10].

We hypothesized that isolated high 1h-PG ≥ 155 mg/dL (8.6 mmol/L) (i)represents an intermediate state between normoglycemia (fasting PG < 100 mg/dL [5.6 mmol/L] and 2-h PG < 140 mg/dL [7.8 mmol/L]) and prediabetes (fasting PG ≥ 100 mg/dL [5.6 mmol/L] and < 126 mg/dL [7.0 mmol/L] or 2-h PG ≥ 140 mg/dL [7.8 mmol/L] and < 200 mg/dL [11.1 mmol/L]) and that (ii)is amenable to greater benefit from LI compared to people with prediabetes in terms of glucose homeostasis, ectopic lipid deposition and incident type 2 diabetes. We were particularly interested in determining whether LI in the high 1h-PG group can reduce insulin resistance, β -cell dysfunction, liver fat content, and visceral adipose tissue volume to levels comparable to those observed in individuals with normal glucose regulation (NGR).

To address these questions, we analyzed the effects of LI in participants in the Tuebingen Lifestyle Intervention Program (TULIP) [11], and compared long-term type

2 diabetes incidence as well as insulin sensitivity and insulin secretion, whole-body fat distribution and visceral adipose tissue volume using MRI and ¹H-MRS-measured liver fat content for the first time between people with normal glucose regulation (NGR), with isolated high 1h-PG or with prediabetes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or both).

2. Research Design and Methods

2.1 Study population

TULIP is a prospective intervention study (2003–2018) in which 413 people with elevated risk of type 2 diabetes received LI [11]. People were defined with elevated risk if they had a family history of type 2 diabetes, body mass index (BMI) ≥ 27 kg/m², 2h-PG diagnostic of IGT or had a history of gestational diabetes. Intensive LI comprising individualized dietary counseling and heart rate-monitored increase of physical activity aimed at body weight reduction of at least 5 % was conducted for 9 months. Comprehensive metabolic phenotyping (5-point OGTT including insulin, C-peptide, triglycerides and free fatty acid measurements, whole body MRI to measure whole body fat distribution, ¹H-MRS measures of liver fat content, spiroergometry to assess maximal oxygen consumption) was performed at baseline and post-intervention at 9 months. In accordance with the Declaration of Helsinki, the study protocol was approved by the relevant authority (Ethics Committee University of Tübingen, 422/2002) and written informed consent was obtained from each person before screening. More details have been published previously [11].

For the present analysis, NGR was defined as FPG < 100 mg/dL (5.6 mmol/L), 2h OGTT glucose < 140 mg/dL (7.8 mmol/L) and 1h-PG < 155 mg/dL (8.6 mmol/L). High 1h-PG was defined as NGR and 1h-PG ≥ 155 mg/dL (8.6 mmol/L). IGR was defined as FPG ≥ 100 mg/dL (5.6 mmol/L) and < 126 mg/dL (7.0 mmol/L), 2h-PG ≥ 140 mg/dL (7.8 mmol/L) and < 200 mg/dL (11.1 mmol/L), or both.

Non-glucose-related criteria included in the present analysis was availability of OGTT data at baseline and after 9 months of LI.

2.2 Outcomes

ADA criteria for the diagnosis of type 2 diabetes were applied [12], and incidences compared between the three groups. Remission to normoglycemia was defined as high 1h-PG and IGR groups achieving NGR at the end of LI. Indexes of insulin sensitivity were calculated from 5-point OGTT data, including Oral Glucose Insulin Sensitivity [13], Matsuda Insulin Sensitivity Index, Adipose Tissue Insulin Sensitivity Index [7], Muscle Insulin Resistance Index and Hepatic Insulin Resistance Index [7]. C-peptide area under the curve (AUC) divided by glucose AUC from 0 to 30 minutes of OGTT ($\text{C-pep}_{\text{AUC 0-30}}/\text{Gluc}_{\text{AUC 0-30}}$) was calculated to evaluate insulin secretion [14]. The Adaptation Index ($\text{C-pep}_{\text{AUC 0-30}}/\text{Gluc}_{\text{AUC 0-30}} \times \text{OGIS}$) estimates β -cell function, i.e. provides a single value that reflects the extent to which insulin

secretion compensates for insulin resistance; The Disposition Index measures β -cell compensatory capacity and was calculated as $[(\Delta\text{Insulin}_{0-30} / 6) / (\Delta\text{Glucose}_{0-30})] \times \text{Matsuda index}$ [13,14]. Whole OGTT C-peptide AUC divided by whole OGTT Insulin AUC ($\text{C-pep}_{\text{AUC } 0-120} / \text{Ins}_{\text{AUC } 0-120}$) was used to assess hepatic insulin clearance [7].

Whole-body T1-weighted MRI images were obtained for each subject to measure visceral adipose tissue (VAT) as previously described [15]. Volume-selective ^1H -MR spectroscopy was used to quantify liver fat content [15].

2.3 Statistical analyses

Linear mixed-effects models were used to analyze longitudinal data, incorporating the model terms group (NGR, high1h-PG, and IGR), timepoint, and their interaction (group $\times$ timepoint), adjusted for age, sex, and BMI (fixed effects). A random intercept was included for each individual. In the model assessing insulin secretion, insulin sensitivity was also added as a fixed effect. For group-wise comparisons of change over the course of LI, one-way ANOVA was performed. Chi-Squared tests with Bonferroni post-hoc correction were performed for categorical variables. Type 2 diabetes incidence was compared via risk ratios and Fischer's exact test using the epitools package, version 0.5-10.1. A Kaplan-Maier curve with log-rank test is also reported. Raw values with mean and error bars or " $\pm$ " representing the 95% confidence interval (CI) being depicted or reported, respectively.

Transitions in glucose status and progression to T2D were analyzed after the 9-month lifestyle intervention. Odds ratios (ORs) for remission were calculated using logistic regression adjusted for age, sex, and BMI.

Receiver operating characteristic analysis was conducted to assess the diagnostic performance of HbA1c, FPG, 1h-PG, and 2h-PG in identifying at-risk individuals, defined as the combined group of IGR and high 1h-PG. The area under the curve, sensitivity, and specificity were calculated and compared using HbA1c as the reference marker.

Statistical analyses were done in RStudio 2024.12.0+467 under R version 4.4.1.

3. Results

3.1 Baseline Differences

Baseline differences are displayed in Table 1. The analysis included 106 people with NGR, 96 with high 1h-PG and 115 with IGR. Of the 115 subjects with IGR, 100 (87.0%) had high 60 min glucose (> 8.6 mmol/L). The distribution of the three groups after incorporating HbA1c into the diagnostic criteria is detailed in Supplementary Table 1, resulting in 64 NGR, 50 high 1h-PG, 196 IGR, and 7 newly identified T2D cases.

The high 1h-PG group was older (46.9 ± 11.4 years) than the NGR group (41.6 ± 11.8 years, $p = 0.0029$). The percentage of males was higher in high 1h-PG group (43.8%) compared to NGR group (27.4%, $p = 0.049$) (Table 1). Insulin sensitivity index was lower in high 1h-PG group (15.9 ± 7.93) compared to NGR group (22.1 ± 10.2 , $p < 0.001$) (Figure 1A), and the Adaptation Index reflecting β -cell function was lower in high 1h-PG group ($26,500 \pm 12,900$, NGR: $40,700 \pm 19,600$, $p < 0.001$) (Figure 1C). Intrahepatic lipid content (IHL) did not differ significantly between NGR ($3.58 \pm 3.50\%$) and the high 1h-PG group ($5.25 \pm 5.35\%$, $p = 0.085$) (Figure 1G), while visceral adipose tissue was higher in the high 1h-PG group (3.51 ± 2.08 L) compared to NGR group (2.45 ± 1.76 L, $p = 0.0013$) (Figure 1E).

Age was higher in the IGR group (47.7 ± 12.1 years) compared to NGR group (41.6 ± 11.8 years, $p < 0.001$). The percentage of males was higher in IGR (42.2%) compared to NGR group (27.4%, $p = 0.049$) (Table 1). Insulin sensitivity (IGR: 12.8 ± 7.05 , NGR: 22.1 ± 10.2 , $p < 0.001$) (Figure 1A), as well as β -cell function (IGR: $20,900 \pm 13,300$, NGR: $40,700 \pm 19,600$, $p < 0.001$) (Figure 1C) were lowest in the IGR group. IHL (Figure 1G) and visceral adipose tissue (VAT) (Figure 1E) was highest in the IGR group (IHL: IGR: $8.22 \pm 8.13\%$ NGR: $3.58 \pm 3.50\%$, $p < 0.001$, VAT: IGR: 3.68 ± 2.12 L, NGR: 2.45 ± 1.76 L, $p < 0.001$).

Insulin sensitivity was lower in the IGR group (12.8 ± 7.05) compared to high 1h-PG group (15.9 ± 7.93 , $p = 0.008$) (Figure 1A). β -cell function was lower in IGR ($20,900 \pm 13,300$) than high 1h-PG ($26,500 \pm 12,900$, $p = 0.011$) group (Figure 1C). IHL was higher in IGR ($8.22 \pm 8.13\%$) compared to the high 1h-PG ($5.25 \pm 5.35\%$, $p = 0.0033$) group (Figure 1G), while VAT was similar ($p=0.57$) (Figure 1E).

Baseline insulin sensitivity and β -cell function were intermediate in the high 1h-PG group between NGR and IGR groups (Figure 1A and 1C). While VAT was similarly elevated in both dysglycemic groups (1h-PG and IGR) (Figure 1E), IHL was higher in IGR group than in high1h-PG group (Figure 1G).

3.2 Differences after LI and Trajectories

Data after the LI are given in Table 2. Weight loss outcomes were comparable across all baseline groups, with 19.4% (14/72) in NGR, 26.3% (20/76) in high 1h-PG, and 27.1% (26/96) in IGR achieving a body weight reduction $\geq 5\%$ following the 9-month lifestyle intervention (Supplementary Figure 2). Following LI, both insulin sensitivity (IGR: 15.65 ± 9.78 vs. NGR: 22.76 ± 10.85 , $p < 0.001$) (Figure 1B) and β -cell function (IGR: $24,549.97 \pm 16,765.08$ vs. NGR: $42,244.17 \pm 23,793.44$, $p < 0.001$) (Figure 1D) were higher in people with NGR compared to IGR. While hepatic lipid content in the high 1h-PG group improved to levels comparable to the NGR group ($p > 0.99$) (Figure 1H), VAT remained lower in the NGR group (2.00 ± 1.61 L) compared to the IGR group (3.49 ± 2.29 L, $p = 0.046$) (Figure 1F).

Thus, insulin sensitivity (IGR: 15.65 ± 9.78 , high 1hPG: 19.41 ± 8.92 , $p = 0.035$) (Figure 1B) and β -cell function (IGR: 24549.97 ± 16765.08 , 1hPG: 34005.57 ± 18639.00 , $p = 0.013$) (Figure 1D) remained higher in high 1h-PG group compared to IGR group after LI and did not differ significantly between the NGR and the high 1h PG group. The hyperbolic relationship between insulin sensitivity and insulin secretion is shown in Figure 1I.

At the end of the 9-month intervention, 105 of 244 participants (43.0%) achieved remission to NGR, while 2 individuals (0.8%), both from the IGR group, developed T2D. Remission to normoglycemia occurred more often in the high 1h-PG group compared to IGR group (OR: 2.18; 95%CI: [1.13 - 4.28], $p = 0.021$) (Table 3).

Risk of T2D up to 12 years of follow-up was 80% (37 - 96 %, $p = 0.005$) lower in the high 1h-PG group compared to the IGR group (Figure 2).

In receiver operating characteristic analysis, 1h-PG demonstrated the highest diagnostic performance for identifying IGR and high 1h-PG individuals (AUC = 0.964), significantly exceeding that of HbA1c ($\Delta AUC = 0.375$, $P < 0.0001$; Supplementary Table 2) and outperforming both FPG and 2h-PG, further supporting 1h-PG in accurately detecting early dysglycemia.

4. Discussion

Our findings demonstrate that isolated high 1h-PG, defines a distinct pathophysiological intermediate state between NGR and IGR. This condition is characterized by a progressive decline in insulin sensitivity and β -cell function, as measured by the adaptation index, from NGR to high 1h-PG to IGR, accompanied by a corresponding increase in ectopic fat accumulation in the liver and visceral adipose tissue. Furthermore, individuals with high 1h-PG exhibit a unique metabolic phenotype that is particularly responsive to LI. Specifically, this group demonstrates a high likelihood of achieving glycemic remission to normoglycemia, including normalization of 1h-PG, through restoration of insulin sensitivity and β -cell function. Notably, the incidence of type 2 diabetes following LI was significantly lower in individuals with high 1h-PG compared to those with IGR over up to 12 years of follow up, underscoring the clinical relevance of 1h-PG as a target for early intervention.

In individuals with high 1h-PG, LI led to an improvement of insulin sensitivity and β -cell function to levels comparable to those observed in the NGR group, an outcome not achieved in the IGR group. In addition, IHL content decreased to NGR-equivalent levels in the high 1h-PG group, whereas VAT remained intermediate between NGR and IGR, at least in numerical terms. These favorable metabolic trajectories translated into a twofold higher likelihood of achieving remission to NGR, including normalization of 1h-PG, following LI, and an 80% reduction in the long-term risk of developing type 2 diabetes compared to the IGR group.

Recent data from South Korea also confirm that in people with high 1h-PG but without IGR, insulin resistance and β -cell dysfunction are more pronounced than in those with NGR, yet less severe than in individuals with IGR. Body fat distribution was not assessed in that study [16]. The authors concluded that high 1h-PG “may provide an opportunity for early intervention to preserve β -cell function.”[16] Building upon this premise, our present study extends these findings by demonstrating that LI is more effective in individuals with elevated 1h-PG compared to people with IGR at restoring the underlying pathophysiological disturbances toward normal. Specifically, LI in this group more effectively restores insulin sensitivity and β -cell function, facilitates remission to NGR, and reduces the long-term risk of developing type 2 diabetes. These findings support the interpretation that 1h-PG is a clinically actionable biomarker that defines a critical window for preventive intervention targeting the core defects driving diabetes pathogenesis.

Previous data showed that high 1h-PG is superior to current diagnostic criteria in predicting future type 2 diabetes [17]. In fact, the incidence of type 2 diabetes was higher in people with high 1h-PG than in people with isolated IFG, isolated IGT or both [18]. Additionally, previous data showed that most people (81%) with a high 1h-PG developed IGT in the long term [19]. Furthermore, high 1h-PG was associated with an increased risk of microvascular complications, cardiovascular disease, and mortality [20]. Moreover, given the relatively higher β -cell function in people with isolated high 1h-PG compared to IGR suggested that initiating LI in these people holds the potential to recover β -cell function at an earlier stage of the disease [2]. Prevention of type 2 diabetes has been demonstrated to be more successful when β -cell function is preserved [21]. We also report higher β -cell function in the high 1h-PG group than in the IGR group at baseline, likely contributing to improved prevention of type 2 diabetes compared to the IGR group. In addition, we show for the first time that after LI, β -cell function in the high 1h-PG group was still higher than in IGR group, confirming greater potential for recovery of β -cell function.

Our data also demonstrate that individuals with high 1h-PG exhibit increased hepatic lipid content compared to those with NGR. Improvement in hepatic steatosis and β -cell function has been recognized as a critical component of type 2 diabetes remission [22]. Current hypotheses suggest that reduction in hepatic lipid content contributes to subsequent decreases in pancreatic lipid accumulation, reducing VLDL-palmitate secretion thereby facilitating recovery of β -cell function, the central mechanism underlying diabetes remission [22]. In individuals at risk for type 2 diabetes, LI has been shown to enhance insulin secretion, particularly in those with impaired β -cell function and elevated hepatic lipid content [23,24]. In the present study, hepatic lipid content was elevated in the IGR group and tended to be increased in the high 1h-PG group at baseline. LI reduced hepatic lipid content to comparable levels to NGR.

Conversely, VAT was similarly elevated in the 1h-PG and IGR groups at baseline. After LI, VAT in the high 1h-PG group improved to levels comparable to the NGR group, which was not observed in the IGR group. VAT reduction has been associated with favorable metabolic outcomes, especially in prediabetes [7]. Thus, the present data also support an important role for VAT reduction the beneficial effect of LI in high 1h-PG.

Higher insulin sensitivity is predictive of favorable LI outcome [21]. Weight loss-induced prediabetes remission, which is highly effective in preventing type 2 diabetes,

critically depends on improved insulin sensitivity [7] while non weight loss dependent prediabetes remission depends on both, improved insulin sensitivity and secretion [25]. We report that insulin sensitivity was less impaired in the high 1h-PG group than in the IGR group. Trajectories of insulin sensitivity were similar between high 1h-PG and IGR groups, and differences persisted after LI. After LI, insulin sensitivity in high 1h-PG group were restored to similar levels as the NGR group.

Achieving prediabetes remission is an emerging goal in type 2 diabetes prevention [25-29]. Prediabetes remission is associated with better renal and microvascular profiles with long-term follow-up [30,31]. We demonstrate that individuals with high 1h-PG are more likely to achieve remission to normoglycemia, attributable to normalization of insulin sensitivity and β -cell function. Importantly, our findings suggest that achieving normoglycemia, including normal 1h-PG, at an early stage of metabolic dysfunction confers greater protection against future onset of type 2 diabetes. Therefore, 1h-PG represents a clinically actionable biomarker that identifies a critical window of opportunity to reverse the core pathophysiological defects of prediabetes and diabetes—namely, insulin resistance and impaired β -cell function—which are also key predictors of future complications.

Our study has limitations. They include the retrospective nature of the present analysis that may have precluded additional mechanistic findings due to different sample size calculations in the original trial. As the original trial was conducted in a single study center in south-western Germany, consideration is warranted when generalizing findings to other ethnicities [11]. However, data from other groups, e.g. in Asia, observed clinical outcomes that confirm our findings [16].

In conclusion, we demonstrate that high 1h-PG characterizes a distinct metabolic phenotype that is particularly responsive to LI. Specifically, these individuals show a high likelihood of achieving remission (i.e., return to NGR, including 1h-PG) through restoration of insulin sensitivity and β -cell function and reduction of hepatic fat content. The identification of high 1h-PG thus provides a critical opportunity to reverse key pathophysiological processes driving the progression to type 2 diabetes and its associated complications. Our findings underscore the clinical relevance of routinely performing an OGTT with specific evaluation of the 1h-PG value in people at risk.

5. Article Information

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5.2 Duality of Interest

No potential conflicts of interest relevant to this article were reported.

5.3 Author Contributions and Guarantor Statement

A.L.B: Conceptualization, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition. M.B.: Conceptualization, Writing – Reviewing & Editing, Supervision. Y.W.: Formal Analysis, Validation, Data Curation, Writing – Visualization & Review & Editing. A.S.: Formal Analysis, Data Curation, Writing – Original Draft, Visualization. Y.C.: Validation, Data Curation, Writing – Review & Editing. J.M., F.S., N.S., K.K. and A.F.: Methodology, Investigation, Writing – Review & Editing. R.JvS, L.S, S.K., and H.P.: Writing - Review & Editing.

A.S., Y.W., and Y.C. had full access to all data reported in the study, take responsibility for the integrity of the data and are guarantors of this work. All authors approved the final version of the manuscript.

5.4 Prior Presentation

Parts of this study were submitted for presentation at the ADA's 85th Scientific Sessions, Chicago, IL, 20-23 June 2025 and the EASD's 61st Annual Meeting, Vienna, Austria, 15-19 September 2025.

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	NGR	High 1h-PG	IGR	p-value	post-hoc comparison	p-value
	(N=106)	(N=96)	(N=115)			
Age [years]					IGR - NGR	<0.001
Mean [SD]	41.6 [11.8]	46.9 [11.4]	47.7 [12.1]	<0.001	IGR - 1hPG	0.63
					NGR - 1hPG	0.0029
Sex [% male]					IGR - NGR	0.049
Mean [SD]	0.274 [0.448]	0.438 [0.499]	0.422 [0.496]	0.025	IGR - 1hPG	0.82
					NGR - 1hPG	0.049
BMI [kg/m²]					IGR - NGR	0.057
Mean [SD]	29.3 [5.49]	30.5 [5.34]	31.2 [7.31]	0.061	IGR - 1hPG	0.39
					NGR - 1hPG	0.32
Fasting Glucose [mmol/L]					IGR - NGR	<0.001
Mean [SD]	4.95 [0.309]	5.15 [0.295]	5.61 [0.510]	<0.001	IGR - 1hPG	<0.001
					NGR - 1hPG	<0.001
Glucose 60 min [mmol/L]					IGR - NGR	<0.001
Mean [SD]	7.06 [1.08]	10.1 [1.08]	10.6 [2.11]	<0.001	IGR - 1hPG	0.016
					NGR - 1hPG	<0.001
Glucose 120 min [mmol/L]					IGR - NGR	<0.001
Mean [SD]	5.78 [0.854]	6.49 [0.883]	8.09 [1.63]	<0.001	IGR - 1hPG	<0.001
					NGR - 1hPG	<0.001
Insulin Sensitivity Index					IGR - NGR	<0.001
Mean [SD]	22.1 [10.2]	15.9 [7.93]	12.8 [7.05]	<0.001	IGR - 1hPG	0.008
					NGR - 1hPG	<0.001
C-Peptide / Glucose 0-30 AUC [pmol/mmol]					IGR - NGR	0.14
Mean [SD]	201 [72.8]	185 [68.9]	182 [70.4]	0.101	IGR - 1hPG	0.8
					NGR - 1hPG	0.19
Adaptation Index of β-cell function					IGR - NGR	<0.001
Mean [SD]	40700 [19600]	26500 [12900]	20900 [13300]	<0.001	IGR - 1hPG	0.011
					NGR - 1hPG	<0.001
Hepatic lipid content [%]					IGR - NGR	<0.001
Mean [SD]	3.58 [3.50]	5.25 [5.35]	8.22 [8.13]	<0.001	IGR - 1hPG	0.0033
					NGR - 1hPG	0.085

Visceral adipose tissue [L]					IGR - NGR	<0.001
Mean [SD]	2.45 [1.76]	3.51 [2.08]	3.68 [2.12]	<0.001	IGR - 1hPG	0.57
					NGR - 1hPG	0.0013
Fasting Triglycerides [mg/dL]					IGR - NGR	0.0013
Mean [SD]	93.7 [69.8]	121 [91.5]	136 [94.9]	0.002	IGR - 1hPG	0.23
					NGR - 1hPG	0.075
Fasting Free Fatty Acids [μmol/L]					IGR - NGR	<0.001
Mean [SD]	595 [208]	667 [321]	739 [253]	<0.001	IGR - 1hPG	0.11
					NGR - 1hPG	0.11
Disposition index					IGR - NGR	0.043
Mean [SD]	10.5 [19.6]	3.38 [1.47]	2.76 [1.78]	<0.001	IGR - 1hPG	> 0.99
					NGR - 1hPG	0.102

Table 1:

Baseline characteristics. Means and standard deviation are reported. P values are extracted from ANOVA and Bonferroni post-hoc correction for numeric variables and Fischer's Exact test with Bonferroni post-hoc correction for categorical variables

Variable	Unit	NGR		High 1hPG		IGR		NGR - IGR	IGR - 1hPG	NGR - 1hPG
		Mean (SD)	Change from baseline (SD)	Mean (SD)	Change from baseline (SD)	Mean (SD)	Change from baseline (SD)			
BMI	kg/m ²	28.03 (5.32)	-1.26 (7.64)	29.55 (4.99)	-0.97 (7.31)	29.90 (5.94)	-1.35 (9.42)	0.17	> 0.99	0.75
Fasting Glucose	mmol/L	4.95 (0.40)	0 (0.51)	5.13 (0.42)	-0.02 (0.52)	5.45 (0.50)	-0.16 (0.71)	< 0.001	< 0.001	0.38
60 min Glucose	mmol/L	7.39 (1.63)	0.33 (1.96)	9.22 (1.99)	-0.84 (2.26)	9.97 (2.19)	-0.6 (3.04)	< 0.001	0.018	< 0.001
120 min Glucose	mmol/L	5.78 (1.06)	0 (1.36)	6.55 (1.40)	0.06 (1.65)	7.45 (1.68)	-0.64 (2.34)	< 0.001	< 0.001	0.0036
Insulin Sensitivity Index	arbitrary units	22.76 (10.85)	0.65 (14.87)	19.41 (8.92)	3.53 (11.94)	15.65 (9.78)	2.89 (12.06)	< 0.001	0.035	0.12
C-pep _{AUC 0-30} /Gluc _{AUC 0-30}	pmol/mmol	195.15 (66.33)	-6.24 (98.45)	180.40 (61.37)	-4.35 (92.27)	177.15 (67.53)	-5.05 (97.57)	< 0.001	0.47	0.010
Adaptation Index	arbitrary units	42244 (23793)	1544 (30044)	34006 (18639)	7506 (36341)	24550 (16765)	3650 (47417)	< 0.001	0.013	0.078
Liver fat content	%	3.62 (7.67)	0.04 (8.43)	3.40 (3.44)	-1.85 (6.36)	5.46 (5.27)	-2.76 (9.69)	> 0.99	> 0.99	> 0.99
Visceral adipose tissue	L	2.00 (1.61)	-0.45 (2.39)	2.74 (1.65)	-0.77 (2.65)	3.49(2.29)	-0.19 (3.12)	0.046	0.98	0.98
Fasting Triglycerides	mg/dL	85.59 (48.75)	-7.55 (82.45)	111.83 (57.37)	2.13 (127.29)	120.88 (92.63)	-11.44 (139.89)	0.50	> 0.99	0.74
Fasting free fatty acids	μmol/L	551.20 (183.01)	-48.49 (275.52)	568.64 (189.72)	-76.36 (362.27)	597.56 (215.89)	-127.02 (327.19)	0.29	> 0.99	0.67
Disposition index	arbitrary units	12.8 (32.1)	2.3 (37.6)	4.4 (2.9)	1.1 (3.3)	2.8 (3.7)	1.1 (4.1)	0.010	> 0.99	0.031

Table 2: Key metabolic parameters post-intervention. Means and standard deviation are reported. P values are extracted from linear mixed effects models including baseline and post-intervention measurements.

Group	No. of participants at 9 months	9 months glucose status, cases (%)				Incidence of remission to NGR	
		NGR	High 1h-PG	IGR	T2D	OR (95% CI)	P value
Overall	244	105 (43.0)	57 (23.4)	80 (32.8)	2 (0.8)	/	/
NGR	72	53 (73.6)	11 (15.3)	8 (11.1)	0 (0)	/	/
High 1h-PG	76	30 (39.5)	25 (32.9)	21 (27.6)	0 (0)	2.18 (1.13 - 4.28)	0.021
IGR	96	22 (22.9)	21 (21.9)	51 (53.1)	2 (2.08)	1.00 (ref)	ref

Table 3:

Transitions in glucose status within each group after the 9-month intervention

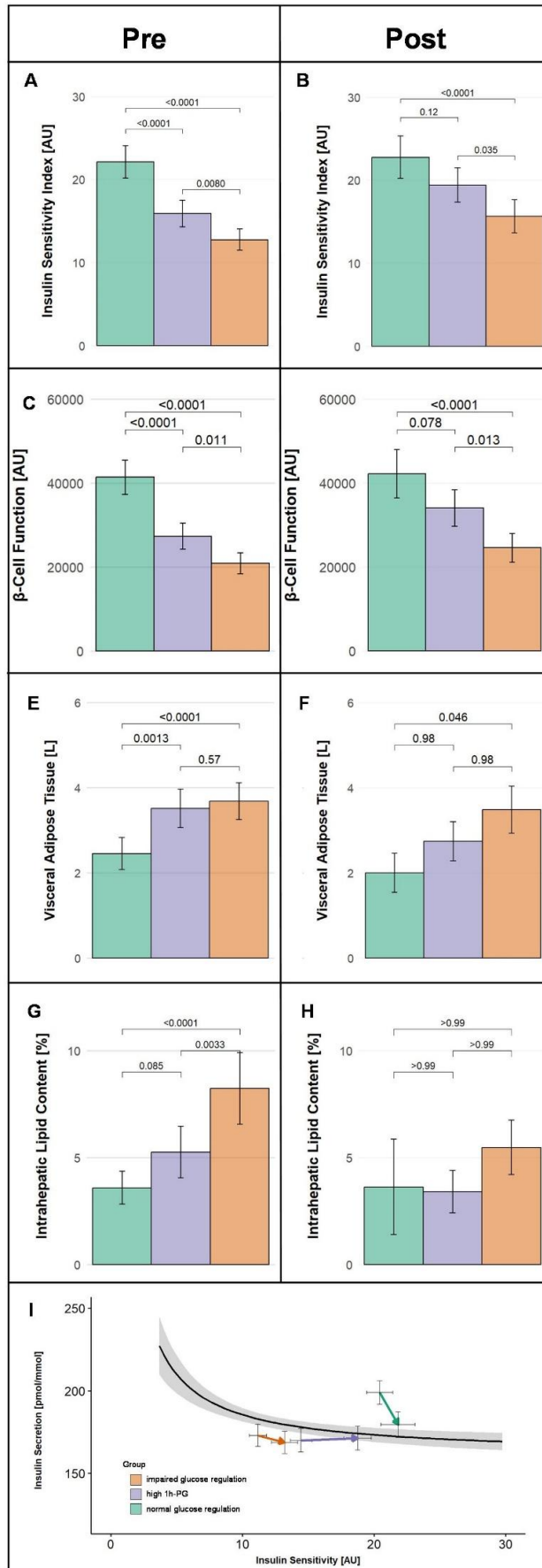
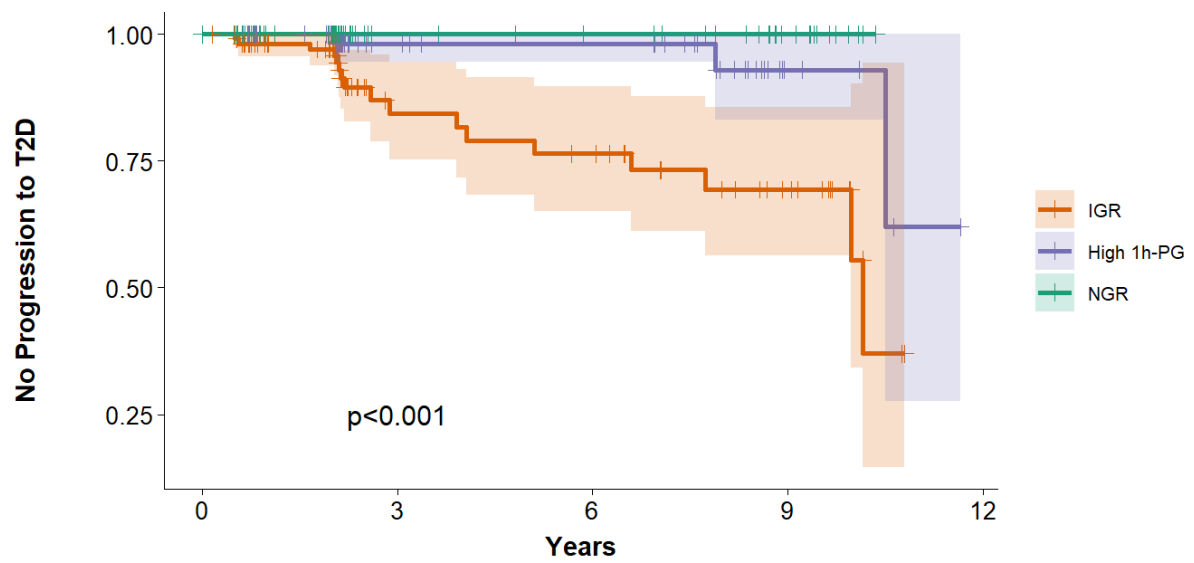


Figure 1: Bar graphs of key metabolic parameters at baseline and after LI in NGR (green), high 1h PG (violet) and IGR (orange) groups. A) Insulin Sensitivity Index

baseline; B) Insulin Sensitivity Index after LI; C) Adaptation Index reflecting β -cell function baseline; D) Adaptation Index reflecting β -cell function after LI; E) visceral adipose tissue volume baseline; F) visceral adipose tissue volume after LI; G) Intrahepatic Lipid Content baseline; H) Intrahepatic Lipid Content after LI; I) hyperbolic relationship between insulin sensitivity and insulin secretion (unadjusted for insulin sensitivity). Error bars indicate 95% confidence interval. P values are extracted from linear mixed effects models and Bonferroni post-hoc correction.



At Risk					
IGR	115	32	28	13	0
High 1h-PG	96	28	25	5	0
NGR	106	26	23	11	0
Events					
IGR	0	10	13	15	17
High 1h-PG	0	1	1	2	3
NGR	0	0	0	0	0

Figure 2:

Kaplan-Meier-Curve of type 2 diabetes incidence during follow-up.