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Insulin Resistance Treatment with Balanced Personalized Nutrition to Improve Insulin Sensitivity for Prediabetes Remission and Diabetes Type 2 Reversal with Reduction of Risks for Related Chronic Disease

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Introduction

Insulin sensitivity, as a key measure of metabolic health and hormonal balance, plays a crucial role in metabolic disease with impaired insulin signaling also described as insulin resistance (Zhao et al., 2023). The problem of insulin resistance as a hormonal imbalance due to a changed metabolism is gaining increasing international attention and can be referred to as new epidemic of the 21st century (Zyoud et al., 2022). Insulin resistance affects an estimated 40% of people aged 18–48. Half of the affected people are not overweight (Parcha et al., 2022).

The American Diabetes Association has newly defined type 2 diabetes as a progressive loss of adequate insulin secretion by β cells against the background of insulin resistance (Draznin et al., 2022). Diabetes is a high-risk metabolic state, where affected individuals can lose from 3.3 to 18.7 years of their life expectancy on average (Mallory et al., 2015). If an individual is affected with diabetes type 2 early in their life, every decade of earlier diagnosis of diabetes is associated with about 3–4 years of lower life expectancy (Kaptoge et al., 2023). The quality of life is reduced in individuals with diabetes type 2 as well as in individuals with insulin resistance (Arditi et al., 2019; Kazukauskiene et al., 2021).

The insulin resistance not only affects the progress of diabetes type 2 but also cardiovascular risks. The presence of insulin resistance and hormonal imbalance increases the incidence of sudden death or heart attack (Devesa et al., 2023). Especially the obesity-related risks of cardiovascular diseases are mediated by insulin resistance (Tian et al., 2022). This may explain altogether why cardiovascular mortality is still excessively high, despite the considerable progress in the prevention and treatment of cardiovascular diseases (Fazio et al., 2024). Alzheimer's (Sun et al., 2023), kidney disease (Kunutsor et al., 2024), hypertension (Miao et al., 2024), depression (Watson et al., 2021), arthritis (Liu et al., 2024), cancer (Marmol et al., 2023) and other non-communicable diseases are further promoted via insulin resistance. Following these findings, it is important to prevent the further spreading of insulin resistance and to establish a treatment.

Insulin resistance develops mostly due to bad nutritional and lifestyle choices (Mirabelli et al., 2020). A poor diet containing too much fat and sugar is the main cause of insulin resistance (Hernandez et al., 2017). This reduces the uptake of sugar into the cells and thus contributes to insulin resistance (von Frankenberg et al., 2017). One main contributor to insulin resistance are elevated triglycerides. Even mild triglyceride accumulation because of malnutrition impairs glucose tolerance (Trico et al., 2022) and reduces insulin sensitivity in parallel with reduced islet β cell function (Ma et al., 2020) and β cell exhaustion (Grubelnik et al., 2022). Elevated triglyceride levels correlate with impaired β cell function with reduced insulin secretion, according to Chen and Wen (2022) and Natali et al. (2017). Over time insulin resistance is build-up (Tian et al., 2023), resulting in the affected person developing prediabetes via compensatory hyper insulin secretion with subsequent β cell dysfunction (Shimodaira et al., 2014) and exposing them to increased type 2 diabetes risks (Ahmed et al., 2021). Of the Swiss population, 31% are recognized as insulin-resistant with prediabetic metabolic conditions, as observed by Blum et al. (2015). Prediabetes is a high-risk metabolic state that has a high annual conversion rate to diabetes of 5–10% (Tabák et al., 2012).

Triglycerides combined with glucose influence the glucolipotoxicity and insulin secretion, measured by the TyG index (Simental-Mendía et al., 2022). The glucolipotoxicity is referring to the accumulation of saturated fats, especially palmitic acid, leading to glucolipotoxic conditions (Marafie et al., 2019), damaging β cells, impeding insulin secretion (Grubelnik et al., 2022) and affecting the Glucagon-like Peptide 1 (GLP-1) secretion (Hong et al. 2021). The resulting

imbalance of hormones and insulin resistance can be quantified by using the TyG Index (Loped-Jaramillo et al., 2023; Wei et al., 2024) but also highly correlate to the extent of damage to β cells (Chen et al., 2022).

The visceral fat level builds up as a secondary effect following the development of insulin resistance, and hyperinsulinemia may trigger the body weight buildup if unhealthy food selections are maintained over a longer time (Wiebe et al., 2021). Obesity correlates strongly with 21 diseases and thus contributes indirectly to increasing the cost of illness (Kivimäki et al., 2022). According to Wiebe et al. (2022), this correlation between obesity and disease exists only with underlying insulin resistance. Therefore, from a nutritional point of view, enrichment of triglycerides needs to be avoided with adequate nutrition with respect to food ingredients. Triglyceride enrichment follows an endogenous or exogenous enrichment of saturated fatty acids and/or glucose ingestion. Among the saturated fatty acids, palmitic acids are the most dangerous (Annevelink et al., 2023). Glucose and saturated fatty acids intake need to be restricted at a level corresponding to a healthy metabolism. This level may be influenced by sex, age or physical conditions.

We investigated the daily intake of food by insulin-resistant, prediabetic and diabetic individuals with different BMI levels to determine whether there are typical patterns in their eating habits. This would allow to directly counteract these patterns with a dietary pattern that considers the biological needs of the body and uses a personalized approach on the nutrition distribution throughout the day maximizing metabolic health and insulin sensitivity. Thus, achieving a reversal of insulin resistance and diabetes type 2 in the treated individuals.

These findings will contribute to overcome the global metabolic crisis characterized by epidemic metabolic and hormonal imbalance with reduced insulin sensitivity respectively insulin resistance.

Methods

To restore metabolic health, a personalized diet ("EPI Method," according to Rohner (2011); Rohner (2019); Rohner et al. (2021)) was applied to improve insulin sensitivity, normalizing insulin resistance (Fig.4) but also reversing type 2 diabetes (Fig. 5 and 6). The EPI Method consists of two parts, always with a three meal per day diet. For insulin resistance and prediabetes remission, the first part is a hepatic-focused whole food diet and applied for 2 weeks. For type diabetes 2 reversal the first part is 6 weeks longer applied and supported with protein shakes (Protiline® or Modifast®) with selected vegetable intake focused mainly on sulforaphane, betaine, and choline. The second part is for both applications a whole food diet which steers and controls the personalized food intake, and is digitally supported on a molecular level for the individual threshold values of selected nutrients, calculated not just for the key influencing macro nutrition molecules of saturated fats, glucose, fiber, and proteins, but also for selected micronutrients, geared to achieve optimal TyG and TG:HDL values, according to Rohner et al. (2021).

The key molecules related to insulin resistance of the food are digitally calculated for metabolic control. The healthy range of the key food ingredients is estimated and visualized for the client for easy self-control, using the "EPI Method web app". The client can simply follow daily his food selection and is informed about how well he is achieving on a critical food ingredient and energy level the targeted biomarkers. Possible deviations are monitored, and a buddy support system is put in place, for increasing the self-efficacy for continuous optimization.

Supporting Product Formulas Combined with Therapy

Both two parts of the therapy are supported with tailored biochemically active product formulas, namely EPIGENOSAN© and METHYLOSAN©. Epigenosan is a capsuled formula product consisting of mate tea extract, oil of the microalgae schizochytrium, green tea extract, an isoflavone from soja extract, l-arginine, magnesium, niacin, pantothenic acid, folic acid, biotin, and vitamins D, E, B6 and B12. The supplement's key ingredients are combined with L-carnitine L-tartrate, assuring a cofactor for the CPT1 enzyme complex, and is intermittently fed under fasting conditions. L-carnitine supports energy metabolism and counteracts metabolic inflexibility, synchronizing the intermittent fasting method and supporting the functionality of the β-oxidation to accelerate the clearance of triglycerides. The product formula epigenosan is embedded into the diet, according to Rohner (2011).

Epimethylosan is a capsuled formula product based on broccoli extracts standardized for sulforaphane, white asparagus powder and includes choline, magnesium, L-methionine, coenzyme Q10, zinc, vitamins B2, B6 and B12, manganese, chrome, and folic acid mediating the One-carbon metabolism and avoiding undernutrition of key molecules for optimal redox reactions. Epimethylosan is always used together with epigenosan.

Analytics Applied and Calculation of Medical Indices

An electronic 4-day diary was used to analyze the daily food intake of a group of 80 individuals with different BMI (from 19 – 53), gender (34 % were of masculine sex and 64 % were of feminine sex), age, and insulin resistance levels. For the nutritional analysis, the DGExpert program from German Society for Nutrition (DGE) was used.

The daily consumed food in total was compared to a standardized value of BMI 23 and also a standardized ratio of saturated fats: calories of BMI 23, describing the optimal timing of food, calculated as per a proprietary algorithm.

Commonly used analytical methods were applied to determine the measured parameters in the figures in the result section. The TyG index was estimated according to the formula [Ln fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2], as published by Simental-Mendía et al. (2008). The TG:HDL ratio was obtained by dividing the triglyceride level (mg/dl) by the HDL-C level (mg/dl) according to Masson et al. (2016).

Subgroups for Insulin/Prediabetes Remission and Diabetes Type 2 Reversal

The total of 80 individuals analyzed for their dietary pattern (Fig. 1-3) were divided for the therapy into 56 individuals for the insulin resistance/prediabetic remission group (Fig. 4) and 24 individuals for the diabetes reversal group respectively (Fig. 5 and 6). The inclusion criteria for the insulin resistance/prediabetic group were no depressive disorders at the time of application. The inclusion criteria for the diabetes reversal group were to be not older than 70; diagnosed with Type 2 Diabetes for not longer than 7 years; no heart attack history; no depressive disorders at the time of application; no insulin treatment; and BMI ≥ 26. Diabetes reversal was defined as fasting glucose of less than 7.0 mmol/l. The treatment of diabetes was not interrupted reaching diabetes reversal until remission of diabetes 2 was reached as published elsewhere (Rohner et al., 2021).

Statistics

A two-sample t-test for dependent samples (pairwise comparison test) was applied using Excel. Statistical significance was considered at $p < 0.05$.

Results

Typical diurnal dietary pattern found for insulin resistance development, irrespective of BMI

The investigated group of 80 persons showed different insulin sensitivity levels throughout all BMI categories. Of all the participants, 71% showed fasting triglyceride blood values above the threshold of 1.47 mmol/l, and 54% were above the upper threshold of 1.70 mmol/l.

The average daily calorie intake for all four BMI groups (BMI 20–25; BMI 25–29.9; BMI 30–39.9; BMI >40) were similar, namely 1653 kcal/d, 1668 kcal/d, 1563 kcal/d and 1671 kcal/d, respectively. Normalizing these results to a standardized BMI of 23 for healthy eating conditions according to DGE standards, the cohort showed a typical dietary pattern throughout the day for all participants across all BMI categories (Fig. 1). We observed a too-low average calorie intake compared to the standardized BMI of 23. We observed for all participants a higher intake of saturated fatty acids, too-low monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake but an almost normal total fat intake. The waist circumference buildup (visceral fat) as observed irrespective of BMI is expected to be not only correlated to the triglyceride level (Zou et al., 2020) but also to the saturated fat intake (Rosqvist et al., 2014). The palmitic saturated fat fraction intake was on average much above the upper threshold for all participants (on daily average 415% above compared to a standardized BMI of 23) expected to contribute to insulin resistance (Annevelink et al., 2023) and has been recognized to be lipotoxic (Liu et al., 2024). All BMI groups showed sugar intake above the upper threshold, much-too-low fiber intake, and too-low total carb intake. The ratio of carbs per g fiber per g food intake is unfavorable at a too high sugar intake. This points to sugar overnutrition as observed for all participants as one of the drivers for the observed triglyceride build-up and an accumulation of visceral fat mass (Moris et al., 2022). Exceeding saturated fat intake (e.g. palmitic acid) above the upper threshold generates together with exceeding glucose intake and lowered MUFA intake a potential milieu for glucolipotoxicity expected to favor insulin resistance development (Zhen et al., 2017) but also affecting β cell health lowering insulin secretion (Hall et al., 2019) and insulin sensitivity (Liu et al., 2024) disturbing the GLP1 hormonal balance (Hong et al., 2021). Higher saturated fatty acid intake compared to the standardized BMI of 23 is expected to be a key ingredient for promoting triglyceride accumulation, considered a main driver for reduced insulin sensitivity or insulin resistance, respectively, as also observed by von Frankenberg et al. (2017) and Zhen et al. (2017).

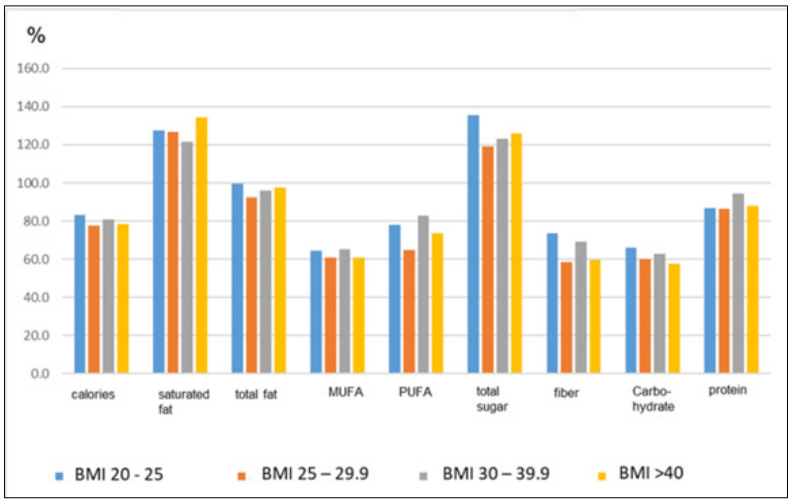

Figure 1: Average values of daily dietary intake of various ingredients in % (100% = optimal intake), grouped by BMI. The investigated group of 80 persons with different BMIs from 19 to 53 presented a similar dietary pattern irrespective of the BMI.

Considering the saturated fatty acid intake as one of the key ingredients for promoting triglyceride buildup led to an analysis of the diurnal intake concerning calories and saturated fat intake. The average intake for calories exceeded the upper threshold compared to a standardized BMI 23 value at dinner but was too low at lunchtime and breakfast (Fig. 2). The average intake for saturated fat intake was observed as highly above the upper threshold at dinner, less at lunchtime, and below the upper threshold at breakfast time (Fig. 2). A typical snacking behavior was observed for almost all participants (90% were snacking in between main meals), expected to contribute to the triglyceride accumulation, increasing risks for insulin resistance (Rasmussen et al., 2002). Snacking in between meals counted on average for a calorie intake of 43.1% of total intake and a saturated total fat intake of 16.1% for a reference BMI of 23 (Fig. 2). Of the participants, 13% did not eat breakfast.

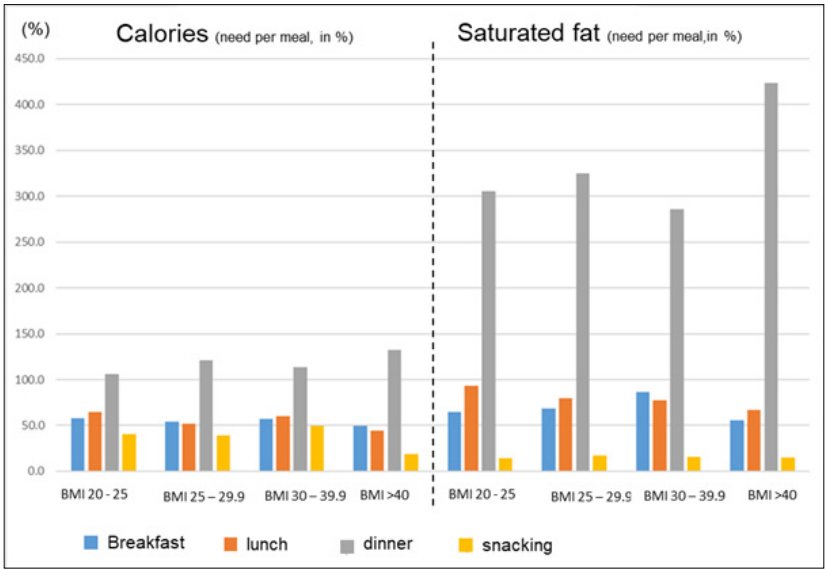

Figure 2: Diurnally distributed intake of total calories and saturated fat for all BMI categories compared to a standardized BMI of 23. This typical diurnal dietary pattern could be observed for almost all participants, irrespective of the BMI category.

The saturated fat coefficient as the ratio between calorie and saturated fat intake was strongly increased in the evening, whereas it was not so in the morning and at lunchtime (Fig. 3).

We did not observe a deviation from this pattern in the different BMI groups and also not on the individual level (Fig. 3), interpreted as a typically diurnal dietary pattern for increased insulin resistance risks, irrespective of BMI.

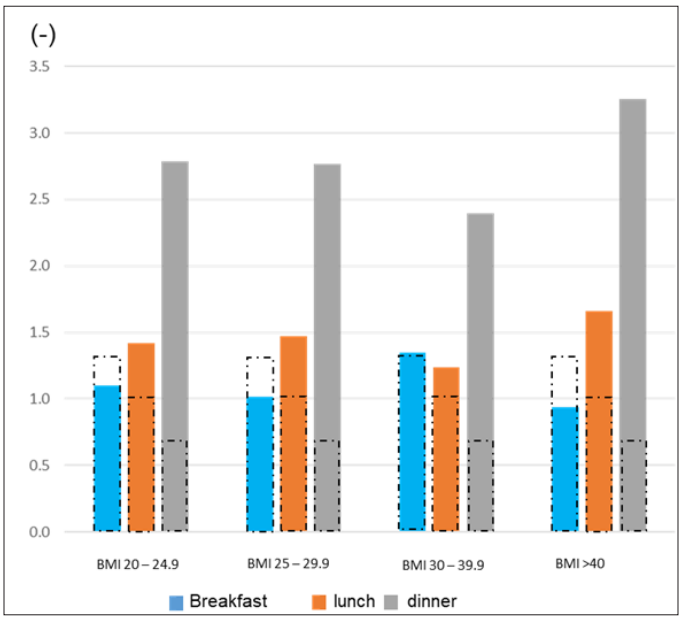

Figure 3: The estimated saturated fat coefficient as the ratio between saturated fat and calory intake for all meals was completely inverted compared to a standardized saturated fat coefficient (= black hatched drawn), as for all BMI categories observed.

Diurnal overfeeding of the organism with saturated fat as per the typical dietary pattern irrespective of the BMI observed (Fig. 3) indicates nutritional conditions mismatching the typical insulin sensitivity pattern (black hatched drawn, Fig. 3) according to Yushino et al. (2014). Diurnal overfeeding as observed is expected to expose the metabolism to increased risk for insulin resistance, irrespective of BMI.

Excess saturated fatty acids, ingested especially at dinner, are expected to feed the de novo lipogenesis as a driver for increased triglyceride generation. A late meal timing was also found by others to coincide with insulin resistance, according to Intemann et al. (2024).

We observe that the higher the triglycerides and lower the HDL values, the higher the insulin resistance risks were, irrespective of the BMI category, presenting a typical signature of insulin resistance. The recognized triggers for insulin resistance with accumulation of saturated fats, especially palmitic acid, have also been recognized as triggers for reduced insulin secretion (Aggarwal et al., 2022; Zhang et al., 2021; Shinhar et al., 2018) and lead to glucolipotoxicity (Marafie et al., 2019), which can damage β cells and impede insulin secretion (Grubelnik et al., 2022). Circulating triglycerides are further recognized as mediating insulin resistance epigenetically (Rönn et al., 2023). We hypothesize that a persistent mismatch of the dietary pattern to the daily biological needs as observed and shown in Fig. 1 and 2 with an increased saturated fat coefficient (Fig. 3) is expected to amplify insulin resistance risks, generating diabetic conditions promoting type 2 diabetes transition over time, irrespective of BMI. This may lead to a phenotypic differentiation to insulin resistance, prediabetes and diabetes not primarily driven by waist circumference or BMI only, in accordance with Eckel et al. (2018), Wiebe et al. (2021) and Abshirini et al. (2020).

A changed food reward triggered by the typical feeding pattern observed with an overflow of saturated fat intake due to an increased ratio of saturated fats: calories (Fig. 3) may drive the food reward to comfort eating as reported by Thanarajah et al. (2023).

Normalizing Insulin Resistance and Remission of Prediabetes with Personalized Nutrition

Restoring the metabolism with timely optimal personalized food ingredients as limited saturated fat (palmitic acid) intake but increased MUFA, PUFA and fiber intake equalizes the observed deviations as in Fig. 1 to 2 and also establishes a good saturated fat coefficient, serving the biological daily profile as well as possible and improving or normalizing the insulin resistance (Fig. 4). It could also reverse prediabetes back to normal with high efficiency, regaining insulin sensitivity in a short time (Fig. 4).

This goal was reached with the "EPI Method," according to Rohner et al. (2021) with a three-meal personalized daily food intake plan for all meals without snacking with most calories and fat ingested in the morning and lunchtime and lower calorie and fat load but high polyphenol load in the evening, using TyG and TG: HDL as a lead biomarker. The personalization is calculated by cutting the increased uptake of saturated and palmitic fat and compensating the deficient macronutritents as observed in a personalized way (see Fig. 1 and 2). The dietary intake of unsaturated fat is increased to improve insulin sensitivity on a personalized level at breakfast and lunch when fatty acid synthesis is minimal (Yushino, 2014) to get the most out of the PUFA intake (Worthmann et al., 2024). MUFAS are extensively used on a personalized level to counteract insulin resistance (Ramos et al., 2023) and (Liu et al. 2024). Avoiding snacking is avoiding malonyl-CoA buildup to activate the fat use for energy supply. For this, optimal in-between mealtimes as reported by Yangbo et al. (2023) are ensured between 4–6 h (Rohner, 2011). Critical cofactors, e.g., L-carnitine and choline, are further supplied as formulas to support the fat metabolism further for energy generation Rohner et al., (2021); Bruls et al., (2019) but also supporting the glutathione metabolism to counteract an impaired mitochondrial fatty acid oxidation (Nguyen et al., 2013). Salad as preload is used to activate the GLP-1 hormones (Indarto et al., 2022). Glucose intake is reduced to the minimum to reduce the formation of palmitic acid (Rasmussen et al., 2002) and PUFA and/or MUFA intake is increased to benefit from the different modulation of insulin sensitivity (Sarabhai et al,. 2022; Errazuriz et al., 2017). Carbs as side dishes are proposed on a personal level to get the fiber intake according to an optimal level needed and also enable enough energy supply from the glucose metabolism (Seidelmann et al., 2018) to counteract insulin resistance if the intake of carbs is too low (Alrashed et al., 2023). Dinner time is used to supply enough polyphenols on a personalized level to counteract the endogenous fat synthesis as reported by Costabile et al. (2022).

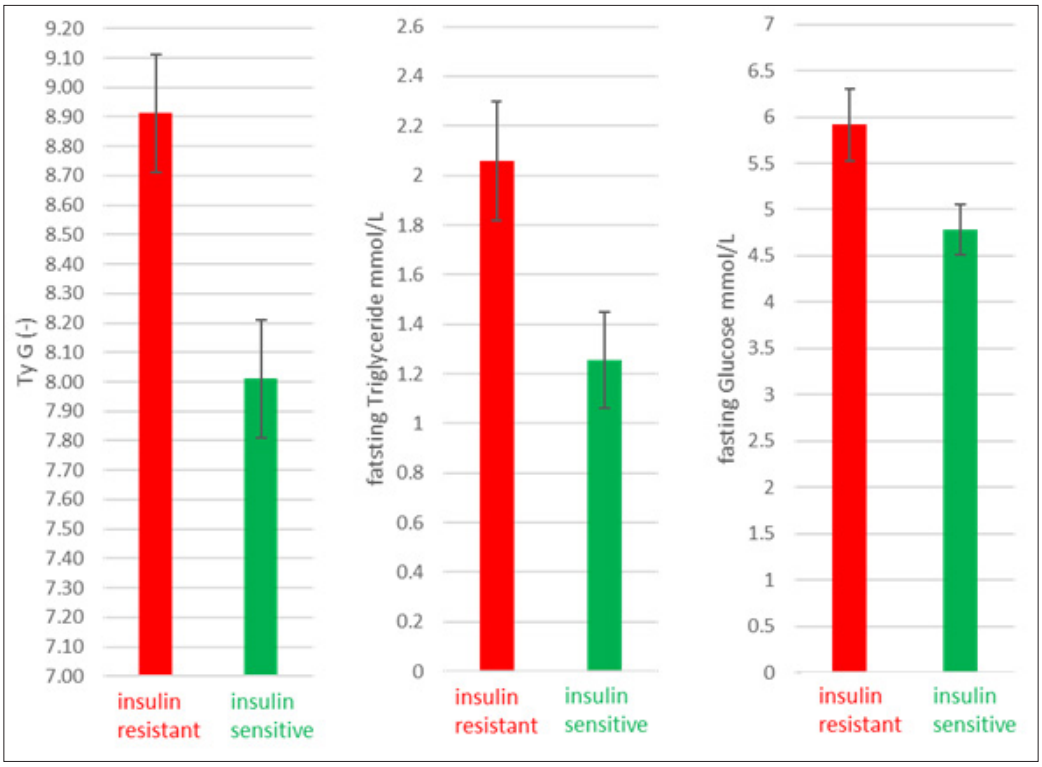

Figure 4: Optimally balanced personalized nutrition reverses insulin resistance quickly, irrespective of BMI (n=56, p<0.001, CI 95%).

Starting with an average TyG Index of 8.9 (threshold of insulin resistance TyG = 8.7), an average TyG Index of 8.0 was reached (equal to 11% improvement), having regained an insulin-sensitive metabolism in 60% of the responders within 10–30 days and 30% within 45 days. Slow responders accounted for 10%. Average triglyceride reduction was estimated at 39% and glucose reduction at 19% within that time. As a side or secondary effect, weight loss was effective on average up to 5% within 30 days. Enhanced insulin sensitivity is important for successful weight loss as found and is in accordance with Clamp et al. (2017). Regaining an insulin-sensitive metabolism at a higher BMI reduces the diabetes risk, according to Cistola and Dwivedi (2022).

The TyG Index could well serve according to our findings as a simple tool for early detection of metabolic imbalance and insulin resistance risks but also to motivate for early lifestyle and eating habits modification making the health progress measurable and visible in accordance with others as the group of de Oliveira et al. (2020) and Sanchez-Escudero et al. (2021). The personal therapy was supported by the visual trending of personally calculated diurnal nutrition with the web app. The web app extracts the relevant food ingredients and calculates the optimal concentration for each meal. This increased the efficacy and adherence with better self-control to maintain the optimal diurnal nutrition path, especially during the evening meal.

These results reveal that personalized nutrition improves predictable insulin sensitivity and reverses insulin resistance fast and sustainably, enabling insulin resistance to be no longer an unmet medical need.

To get out of the global metabolic crisis characterized by epidemic hormonal imbalance with reduced insulin sensitivity, the eating pattern throughout the day should match the biological needs best concerning ingested food ingredients, calories and food intake timing to prevent not only excess of saturated fatty acids and glucose but also triglyceride buildup to prevent or counteract insulin resistance as found. This is preventing type 2 diabetes and reducing heart disease risks (Devesa et al., 2023), gaining healthy lifetime, enables healthy aging and delivers improved quality of life. The centenarian research shows that those 100 years old or even older could bypass the diabetes and heart risks preserving good metabolic health according to Murata S. et al. (2024). They showed in 65-year-olds that good metabolic health with a good hormonal balance from a metabolic view increases the chance of being a centenarian and reaching longevity.

Reversing Type 2 Diabetes with Personalized Nutrition

With our personalized nutrition method, the same dietary ingredients triggering insulin resistance and loss of insulin secretion are treated and eliminated at the same time. The same approach as for treating insulin resistance (Fig. 4) reverses diabetes type 2 (Fig. 5 and 6), regaining an insulin-sensitive metabolism and enables remission of type 2 diabetes on a longer term (Rohner et al., 2021). For diabetic patients, the method is applied with even more stringent liver-centered nutrition than for prediabetes remission with respect to calories, energy and micronutrient density. The saturated fat intake is also more restricted with higher intake in vegetables selected, e.g., for sulforaphane, and also glutathione, improving the GLP1 signal axis (Tian et al., 2024).

The insulin resistance of the initially diabetic patients was reversed within 4 weeks as shown in Fig. 5 as observed.

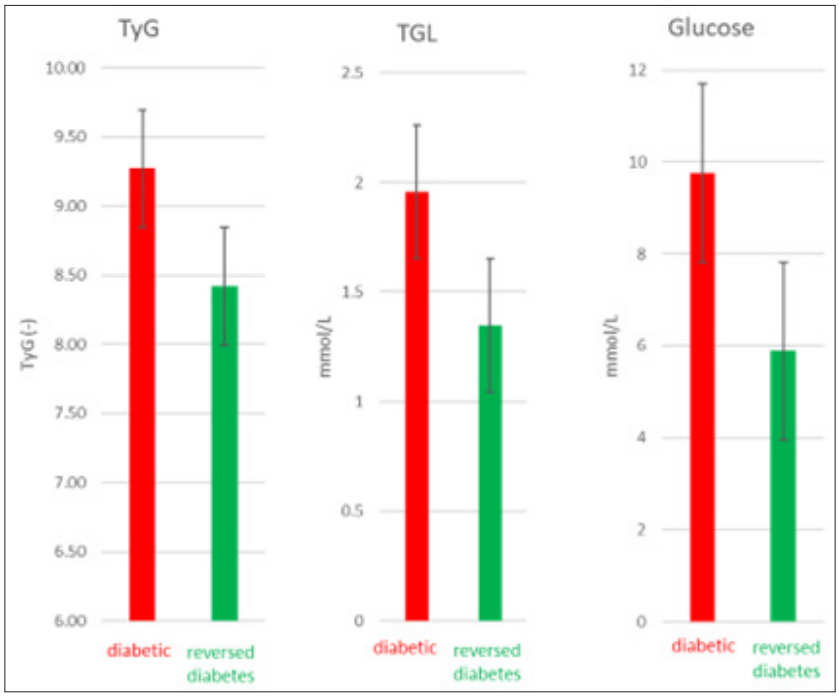

Figure 5: Balanced personalized nutrition with an optimal personal diet reverses insulin resistance quickly in diabetic patients, reversing diabetes quickly, irrespective of BMI (n=24, p<0.001, CI 95%).

Starting with an average TyG Index of 9.8 (threshold of insulin resistance TyG = 8.7), an average TyG Index of 8.4 was reached (equal to 16.6% improvement), having regained an insulin-sensitive metabolism and reversed diabetes type 2 within the first 30 days of application (Fig. 5). Average triglyceride reduction was estimated at 45%, and glucose reduction at 65% within that time. These results reveal personalized nutrition for improving predictable reversing insulin resistance sustainably in diabetic persons, enabling quick diabetes 2 reversal for BMI >26 (Fig. 5).

Compared to patients with insulin resistance and/or prediabetic conditions, the initial insulin resistance is higher in diabetic patients as per the TyG index. Within the same time frame, personalized nutrition is applied with an identical focus on balancing out the excess but also the undernutrition of important macronutrients, feeding nutrition in a timely diurnal optimal manner considering the biological general conditions. Initially, non-diabetic patients are regaining insulin-sensitive conditions on lower TyG values compared to initially diabetic patients within the same time of application.

We observed that the lower the TyG values reached, the lesser the time the patients spent diagnosed as diabetic. Therefore, even though the number of patients is small, we conclude that as the treatment for newly diagnosed patients, the nutritional treatment fits optimally as a new first-hand action for the medical doctor.

Reversing insulin resistance for reversing diabetes and improving β cell function for better insulin secretion fits to the new definition of diabetes given by the American Diabetes Association (Draznin et al., 2022).

Since insulin resistance is observed as an ongoing load to the metabolism due the observed malnutrition (Fig. 1-3), expected leading to hormonal imbalance the longer the malnutrition persists, relieving the metabolism with restriction of the critical food ingredients and gaining insulin sensitivity measured with the TyG results in a fast reversal of diabetes as applied with the EPI Method, measuring the evolving fasting glucose values (Fig.6). Out of 24 persons, 23 could reverse their insulin resistance, regaining an insulin-sensitive metabolism within 4 weeks of application irrespective of BMI (Fig. 6). Diabetes reversal was defined as reaching fasting glucose values of <7.0 mmol/l.

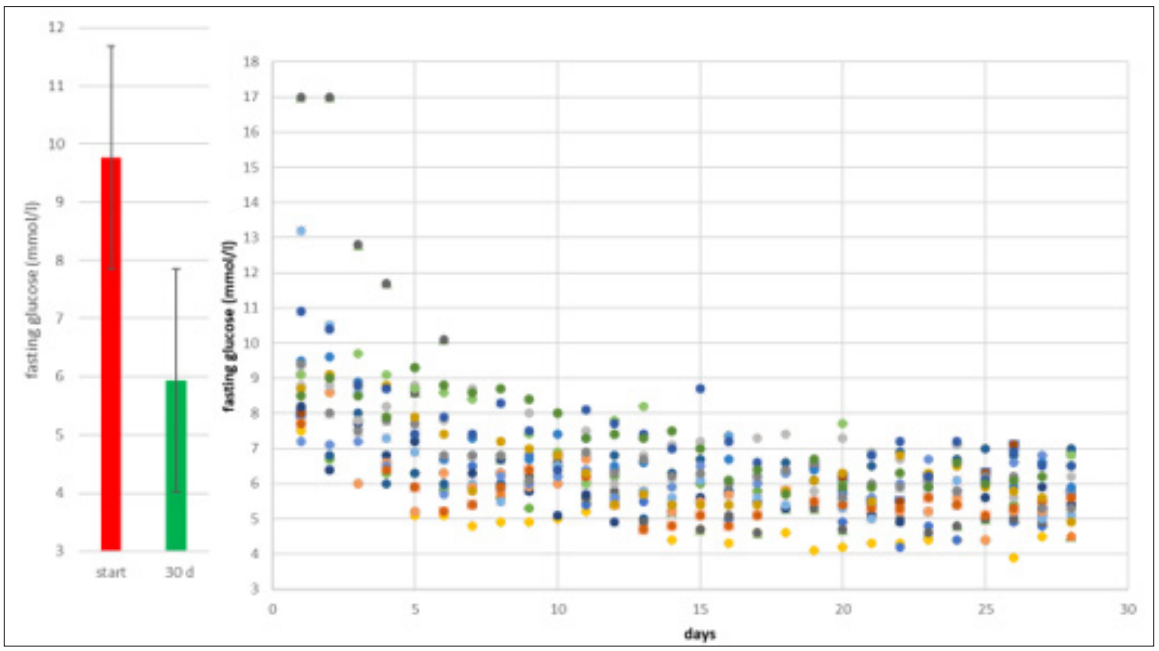

Figure 6: Applying personalized nutrition reverses type 2 diabetes quickly, reaching the threshold value of 7 mmol/l fasting glucose for diabetes reversal within 30 days (39% improvement). Type 2 diabetes remission needs a further 4 months of application in addition. Glycemic medication of the participants involved if applied was omitted from the beginning of the therapy or the latest within 14 days, according to the medical doctor's guidance. Each color point represents a participant with a BMI ranging from 26 to 53 (n=24, p<0.001, CI 95%).

The curve crowd (Fig. 6) is spread at the initial starting value, but the change in glucose/per time is rather similar for all patients involved, which is expected following a typical depletion curve due to relieving of insulin resistance (Fig. 5). If applied for 4 months longer, patients gain remission of diabetes 2 as published elsewhere (Rohner et al., 2021).

These results reveal personalized nutrition as a new first-hand action for reversing newly diagnosed type 2 diabetes focused on insulin resistance treatment, irrespective of the BMI. However, the minimal starting BMI for the therapy is BMI >26 to apply the method as published earlier; see also Rohner et al. (2021). Establishing an insulin sensitive metabolism avoiding insulin resistance by considering nutrition and metabolic health as the cornerstone of modern disease prevention would lower the incidence of type 2 diabetes with reduction of risks for related chronic disease.

Conclusion

Personalized nutrition reversing insulin resistance with TyG and TG: HDL as lead biomarker is according to our results key for regaining and keeping an insulin sensitive metabolism for good metabolic health. We estimate that dietary patterns are more important than BMI for triglyceride accumulation, with increased risk for insulin resistance, prediabetes and type 2 diabetes. We assume that insulin resistance is a signal of a maladjustment to the biological daily nutritional requirements for maximal insulin sensitivity, amplifying the phenotypic differentiation to type 2 diabetes irrespective of BMI. A dietary pattern that meets biological needs as closely as possible with a personalized diet focused on the critical food ingredients normalizes insulin resistance predictably to be no longer an unmet medical need, reverses prediabetes and type 2 diabetes quickly, preventing heart risks and reduces risks for other related chronic disease. Weight loss was effective, with a dietary focus on insulin sensitivity.

Acknowledgement

We acknowledge the scientific assistance of Michèle Rohner and her tireless support, but we also thank our clients for choosing our EPI Method to get rid of insulin resistance and restart a healthy life full of insulin sensitivity. We acknowledge Lieni Füglistaller for his ongoing support as an investor to EGB EpiGeneticBalance AG.

References

1. Zhao, X., An, X., Yang, C., Sun, W., Ji, H., & Lian F. (2023). The crucial role and mechanism of insulin resistance in metabolic disease. *Front Endocrinol (Lausanne), 28*(14), 1149239. DOI: 10.3389/fendo.2023.1149239
2. Zyoud, S. H., Shakhshir, M., Koni, A., Abushanab, A. S., Shahwan, M., Jairoun, A. A., Al Subu, R., Abu Taha, A., & Al-Jabi, S. W. (2022). Mapping the global research landscape on insulin resistance: Visualization and bibliometric analysis. *World J Diabetes, 13*(9), 786–798. DOI: 10.4239/wjd.v13.i9.786
3. Parcha, V., Heindl, B., Kalra, R., Li, P., Gower, B., Arora, G., & Arora, P. (2022). Insulin resistance and cardiometabolic risk profile among nondiabetic American young adults: Insights from NHANES. *J Clin Endocrinol Metab, 1*(107), e25–e37. DOI: 10.1210/clinem/dgab645

4. Draznin, B., Aroda, V. R., Bakris, G., Benson, G., Brown, F. M., Freeman, R., Green, J., Huang, E., Isaacs, D., Kahan, S., Leon, S., Lyons, S. K., Peters, A. L., Prahalad, P., Reusch, J. E. B., & Young-Hyman, D. (2022). Classification and diagnosis of diabetes: American Diabetes Association Professional Practice Committee. *Diabetes Care, 45*(1), S17–S38. DOI: https://doi.org/10.2337/dc22-S002
5. Mallory, M. Y., Leung, M. Y., Pollack, L. M., Colditz, G. A., & Chang, S. H. (2015). Life years lost and lifetime health care expenditures associated with diabetes in the US National Health Interview Survey 1997–2000. *Diabetes Care, 38*(3), 460–468. DOI: 10.2337/dc14-1453
6. Kaptoge, S., Seshasai, S. R. K., Sun, L., Walker, M., Bolton, T., Spackman, S., Atakle, F., Willeit, P., Bell, S., Burgess, S., Pennells, L., Altay, S., Assmann, G., Ben-Sholom, Y., Best, L. G., Bjorkelund, C., Blazer, D. G., Brenner, H., Brunner, E. J… Geleijnse, M. (2023). Life expectancy associated with different ages at diagnosis of type 2 diabetes in high income countries: 23 million person-years of observation. *Lancet Diabetes Endocrinol, 10*(11), 731–742. DOI: http://dx.doi.org/10.1016/S2213-8587(23)00223-1
7. Arditi, C., Zanchi, A., & Peytremann-Bridevaux, I. (2019). Health status and quality of life with diabetes in Switzerland. *Prim Care Diabetes, 13*(3), 233–241. DOI: 10.1016/j.pcd.2018.11.016
8. Kazukauskiene, N., Podlipskyte, A., Varoneckas, G., & Mickuviene, N. (2021). Health-related quality of life and insulin resistance over a 10-year follow-up. *Sci Rep, 11*(1), 24294. DOI: 10.1038/s41598-021-03791-x
9. Devesa, A., Fuster, V., Vazirani, R., García-Lunar, I., Oliva, B., España, S., Moreno-Arciniegas, A., Sanz, J., Perez-Herreras, C., Bueno, H., Lara-Pezzi, E., García-Alvarez, A., de Vega, V. M., Fernández-Friera, L., Trivieri, M. G., Fernández-Ortiz, A., Rossello, X., Sanchez-Gonzalez, J., & Ibanez, B. (2023). Cardiac insulin resistance in subjects with metabolic syndrome traits and early subclinical atherosclerosis. *Diabetes Care, 46*(11), 2050–2057. DOI: 10.2337/dc23-0871
10. Tian, X., Chen, S., Wang, P., Xu, Q., Zhang, Y., Luo, Y., Wu, S., & Wang, A. (2022). Insulin resistance mediates obesity-related risk of cardiovascular disease: A prospective cohort study. *Cardiovasc Diabetol, 21*(1), 289. DOI: 10.1186/s12933-022-01729-9
11. Fazio, S., Mercurio, V., Tibullo, L., Fazio, V., & Affuso, F. (2024). Insulin resistance/hyperinsulinemia: An important cardiovascular risk factor that has long been underestimated. *Front Cardiovasc Med, 13*(11), 1380506. DOI: 10.3389/fcvm.2024.1380506
12. Sun, J., Xie, Z., Wu, Y., Liu, X., Ma, J., Dong, Y., Liu, C., Ye, M., & Zhu, W. (2023). Association of the triglyceride-glucose index with risk of Alzheimer's disease: A prospective cohort study. *Am J Prev Med, 65*(6), 1042–1049. DOI: 10.1016/j.amepre.2023.07.011
13. Kunutsor, S., Seidu, S., Kurl, S., & Laukkanen, J. A. K. (2024). Baseline and usual triglyceride-glucose index and the risk of chronic kidney disease: A prospective cohort study. *Geroscience, 46*(12). DOI: http://dx.doi.org/10.1007/s11357-023-01044-5
14. Miao, H., Zhou, Z., Yang, S., & Zhang, Y. (2024). The association of triglyceride-glucose index and related parameters with hypertension and cardiovascular risk: A cross-sectional study. *Hypertens Res, 47*(4), 877–886. DOI: https://doi.org/10.1038/s41440-023-01502-9
15. Watson, K. T., Simard, J. F., Henderson, V. W., Nutkiewicz, L., Lamers, F., Nasca, C., Rasgon, N., & Penninx, B. W. J. H. (2021). Incident major depressive disorder predicted by three measures of insulin resistance: A Dutch cohort study. *Am J Psychiatry, 178*(10), 914–920. DOI: 10.1176/appi.ajp.2021.20101479
16. Liu, W., Zhu, M., Liu, J., Su, S., Zeng, X., Fu, F., Lu, Y., Rao, Z., & Chen, Y. (2024). Comparison of the effects of monounsaturated fatty acids and polyunsaturated fatty acids on the lipotoxicity of islets. *Front Endocrinol (Lausanne)*, 15, 1368853. DOI: 10.3389/fendo.2024.1368853
17. Liu, Y., Yao, J., Xue, X., Lv, Y., Guo, S., & Wei, P. (2024). Trigylceride-glucose index in the prediction of new-onset arthritis in the general population aged over 45: the first longitudinal evidence from CHARLS. *Lipids in Health and Disease, 23*(1), 79. DOI: 10.1186/s12944-024-02070-8
18. Màrmol, J. M., Carlsson, M., Raun, S. H., Grand, M. K., Sørensen, J., Lang Lehrskov, L., Richter, E. A., Norgaard, O., & Sylow, L. (2023). Insulin resistance in patients with cancer: A systematic review and meta-analysis. *Acta Oncol, 62*(4), 364–371. DOI: 10.1080/0284186X.2023.2197124
19. Mirabelli, M., Russo, D., & Brunetti, A. (2020). The role of diet on insulin sensitivity. *Nutrients, 12*(10), 3042. DOI: 10.3390/nu12103042
20. Hernández, E. A., Kahl, S., Seelig, A., Begovatz, P., Irmler, M., Kupriyanova, Y., Nowotny, B., Nowotny, P., Herder,C., Barosa, C., Carvalho, F., Rozman, J., Neschen, S., Jones, J.G., Beckers, J., Hrabe de Angelis, M., & Roden, M. (2017). Acute dietary fat intake initiates alterations in energy metabolism and insulin resistance. *J Clin Invest, 127*(2), 695–708. DOI: 10.1172/JCI89444
21. von Frankenberg, A. D., Marina, A., Song, X., Callahan, H. S., Kratz, M., Utzschneider, K. M. (2017). A high-fat, high-saturated fat diet decreases insulin sensitivity without changing intra-abdominal fat in weight-stable overweight and obese adults. *Eur J Nutr, 56*(1), 431–443. DOI: 10.1007/s00394-015-1108-6
22. Trico, D., Mengozzi, A., Baldi, S., Bizzotto, R., Olaniru, O., Toczyska, K., Huang, G. C., Seghieri, M., Frascerra, S., Amiel, S. A., Persaud, S., Jones, P., Mari, A., & Natali A. (2022). Lipid-induced glucose intolerance is driven by impaired glucose kinetics and insulin metabolism in healthy individuals. *Metabolism*, 134, 155247. DOI: 10.1016/j.metabol.2022.155247
23. Ma, M., Liu, H., Yu, J., He, S., Li, P., Ma, C., Zhang, H., Xu, L., Ping, F., Li, W., Sun, Q., & Li, Y. (2020). Triglyceride is independently correlated with insulin resistance and islet beta cell function: A study in population with different glucose and lipid metabolism states. *Lipids Health Dis, 19*(1), 121. DOI: https://doi.org/10.1186/s12944-020-01303-w

24. Grubelnik, V., Zmazek, J., Završnik, M., & Marhl, M. (2022). Lipotoxicity in a vicious cycle of pancreatic beta cell exhaustion. *Biomedicines, 10*(7), 1627. DOI: 10.3390/biomedicines10071627
25. Chen, Z. & Wen, J. (2022). Elevated triglyceride-glucose (TyG) index predicts impaired islet beta-cell function: A hospital-based cross-sectional study. Front. *Endocrinol* (Lausanne), 13, 973655. DOI: 10.3389/fendo.2022.973655
26. Natali, A., Baldi, S., Bonnet, F., Petrie, J., Trifirò, S., Tricò, D., & Mari, A. (2017). Plasma HDL-cholesterol and triglycerides, but not LDL-cholesterol, are associated with insulin secretion in non-diabetic subjects. *Metabolism*, 69, 33–42. DOI: 10.1016/j.metabol.2017.01.001
27. Tian, X., Chen, S., Xu, Q., Xia, X., Zhang, Y., Wang, P., Wu, S., & Wang, A. (2023). Magnitude and time course of insulin resistance accumulation with the risk of cardiovascular disease: An 11 year cohort study. *Cardiovascular Diabetology, 22*(1), 339. DOI: 10.1186/s12933-023-02073-2
28. Shimodaira, M., Niwa, T., Nakajima, K., Kobayashi, M., Hanyu, N., & Nakayama, T. (2014). Serum triglyceride levels correlated with the rate of change in insulin secretion over two years in prediabetic subjects. *Ann Nutr Metab, 64*(1), 38–43. DOI: 10.1159/000360012
29. Ahmed, F., Al- Habori, M., Al- Zabedi, E., & Saif-Ali, R. (2021). Impact of triglycerides and waist circumference on insulin resistance and β-cell function in non-diabetic first-degree relatives of type 2 diabetes. *BMC Endocr Disord, 21*(1), 124. DOI: 10.1186/s12902-021-00788-5
30. Blum, J., Aeschbacher, S., Schoen, T., Bossard, M., Pumpol, K., Brasier, N., Risch, M., Risch, L., & Conen, D. (2015). Prevalence of prediabetes according to hemoglobin A1c versus fasting plasma glucose criteria in healthy adults. *Acta Diabetol, 52*(3), 631–632. DOI: 10.1007/s00592-014-0659-y
31. Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., Kivimäki, M. (2012). Prediabetes: A high - risk state for diabetes development. *Lancet, 379*(9833), 2279–2290. DOI: 10.1016/S0140-6736(12)60283-9
32. Simental-Mendía, L. E., Rodríguez-Morán, M., & Guerrero-Romero, F. (2008). The product of fasting glucose and triglycerides as a surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord, 6*(4), 299–304. DOI: http://dx.doi.org/10.1089/met.2008.0034
33. Marafie, S. K., Al-Shawaf, E. M., Abubaker, J., & Arefanian, H. (2019). Palmitic acid induces lipotoxicity promotes a novel interplay between Akt-mTor, IRS-1 and FFAR1 signaling in pancreatic β cells. *Biological research, 52*(1), 44. DOI: 10.1186/s40659-019-0253-4
34. Lopez-Jaramillo, P., Gomez-Arbelaez, D., Martinez-Bello, D., Abat, M. E. M., Alhabib, K. F., Avezum, Á., Barbarash, O., Chifamba, J., Diaz, M. L., Gulec, S., Ismail, N., Iqbal, R., Kelishadi, R., Khatib, R., Lanas, F., Levitt, N. S., Li, Y., Mohan, V., Mony, P. K., Poirier, P…. Yusuf, S. (2023). Association of the triglyceride glucose index as a measure of insulin resistance with mortality and cardiovascular disease in populations from five continents (PURE study): A prospective cohort study. *Lancet Healthy Longev, 4*(1), E23–E33. DOI: 10.1016/S2666-7568(22)00247-1
35. Wei, X., Min, Y., Song, G., Ye, X., & Liu, L. (2024). Association between triglyceride-glucose related indices with the all-cause and cause-specific mortality among the population with metabolic. *Cardiovascular Diabetology, 23*(134), e23–e33. DOI: 10.1186/s12933-024-02215-0
36. Wiebe, N., Ye, F., Crumley, E. T., Bello, A., Stenvinkel, P., Tonelli, M. (2021). Temporal associations among body mass index (BMI), fasting insulin, and systematic inflammation: A Systematic Review and Meta-analysis. *Jama Netw Open, 4*(3), e1263. DOI: 10.1001/jamanetworkopen.2021.1263
37. Kivimäki, M., Strandberg, T., Pentti, J., Nyberg, S. T., Frank, P., Jokela, M., Ervasti, J., Suominen, S. B., Vahtera, J., Sipilä, P. N., Lindbohm, J. V., & Ferrie, J. E. (2022). Body-mass index and risk of obesity-related complex multimorbidity: An observational multicohort study. *Lancet Diabetes Endocrinol, 10*(4), 253–263. DOI: 10.1016/S2213-8587(22)00033-X
38. Wiebe, N., Muntner, P., & Tonelli, M. (2022). Associations of body mass index, fasting insulin, and inflammation with mortality: A prospective cohort study. *Int J Obes, 46*(12), 2107–2113. DOI: 10.1038/s41366-022-01211-2
39. Annevelink, C. E., Sapp, P. A., Petersen, K. S., Shearer, G. C., Kris-Etherton, P. M. (2023). Diet derived and diet related endogenously produced palmitic acid: Effects on metabolic regulation and cardiovascular disease risk. *Journal of Clinical Lipidology, 17*(5), 577–586. DOI: 10.1016/j.jacl.2023.07.005
40. Rohner, M. (2011). Method for Weight Reduction. European Patent EP1962826B1.Retrieved from https://www.thieme-connect.com/products/ejournals/pdf/10.1055/a-1510-8896.pdf
41. Rohner M. (2019). Method for evaluating foods, and nutritional systems for the prevention and treatment of chronic disease. *European Patent EP3166639B1*. Retrieved from https://www.thieme-connect.com/products/ejournals/pdf/10.1055/a-1510-8896.pdf
42. Rohner, M., Heiz, R., Feldhaus, S., & Bornstein, S. R. (2021). Hepatic-metabolite-based intermittent fasting enables a sustained reduction in insulin resistance in type 2 diabetes and metabolic syndrome. *Horm Metab Res, 53*(8), 529–540. DOI: 10.1055/a-1510-8896
43. Simental-Mendía, L. E., Gómez-Díaz, R., Wacher, N. H., & Guerrero-Romero, F. (2022). The Triglycerides and Glucose Index is negatively associated with insulin secretion in young adults with normal weight. *Horm Metab Res, 54*(1), 33-36. DOI: 10.1055/a-1713-7821
44. Masson, W., Siniawski, D., Lobo, M., Molinero, G., & Huerín, M. (2016). Association between triglyceride/HDL cholesterol ratio and carotid atherosclerosis in postmenopausal middle-aged women. *Endocrinol Nutr, 63*(7), 327–332. DOI: 10.1016/j.endonu.2016.04.004
45. Zou, Y., Sheng, G., Yu, M., & Xie, G. (2020). The association between triglycerides and ectopic fat obesity: An inverted U-shaped curve. *PLoS, 15*(11), e0243068. DOI: 10.1371/journal.pone.0243068

46. Rosqvist, F., Iggman, D., Kullberg, J., Cedernaes, J., Johansson, H. E., Larsson, A., Johansson, L., Ahlström, H., Arner, P., Dahlman, I., & Risérus, U. (2014). Overfeeding of polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. *Diabetes, 63*(7), 2356–2368. DOI: 10.2337/db13-1622
47. Moris, J. M., Fitzgibbons, A., Burnam, B., Petty, G., Heinold, C., Timon, C., Koh, Y. (2022). A high carbohydrate-to-fiber ratio is associated with a low diet quality and high fat mass in young woman. *Human Nutrition & Metabolism*, 30, 200163. DOI: http://dx.doi.org/10.1016/j.hnm.2022.200163
48. Hong, J. H., Kim, D. H., & Lee, M. K. (2021). Glucolipotoxicity and GLP-1 secretion. *BMJ Open Diabetes Res Care, 9*(1), e001905. DOI: 10.1136/bmjdrc-2020-001905
49. Yushino, J., Almeda-Valdes, P., Patterson, B. W., Okunade, A. L., Imai, S., Mittendorfer, B., & Klein, S. (2014). Diurnal variation in insulin sensitivity of glucose metabolism is associated with diurnal variation in whole-body and cellular fatty acid metabolism in metabolically normal women. *J Clin Endocrinol, 99*(9), E1666–E1670. DOI: 10.1210/jc.2014-1579
50. Intemann, T., Bogl, L. H., Hunsberger, M., Lauria, F., De Henauw, S., Molnar, D., Moreno, L. A., Tornaritis, M., Veidebaum, T., Ahrens, W., Hebestreit, A. et al. (2024). A late meal-timing pattern is associated with insulin resistance in European children and adolescent. *Pediatric Diabetes*, 24, 6623357. DOI: https://doi.org/10.1155/2024/6623357
51. Aggarwal, R., Peng, Z., Zeng, N., Silva, J., He, L., Chen, J., Debebe, A., Tu, T., Alba, M., Chen, C. Y., Stiles, E. X., Hong, H., Stiles, B. L. (2022). Chronic exposure to palmitic acid down-regulates AKT in β cells through activation of mTOR. *The American Journal of Pathology, 192*(1), 130–145. DOI: 10.1016/j.ajpath.2021.09.008
52. Zhang, M., Yang, C., Zhu, M., Qian, L., Luo, Y., Cheng, H., Geng, R., Xu, X., Qian, C., & Liu, Y. (2021). Saturated fatty acids entrap PDX1 in stress granules and impede islet beta cell function. *Diabetologia, 64*(5), 1144–1157. DOI: 10.1007/s00125-021-05389-4
53. Shinhar, N., Marcoviciu, D., & Dicker, D. (2018). Reduction in Serum Triglyceride levels in diabetic patients may result in decreased insulin dependence and disease progression. *IMAJ, 20*(6), 363–367. Retrieved from https://pubmed.ncbi.nlm.nih.gov/29911757/
54. Rönn, T., Perfilyev, A., Jönsson, J., Eriksson, K. F., Jørgensen, S. W., Brøns, C., Gillberg, L., Vaag, A., Stener-Victorin, E., & Ling, C. (2023). Circulating triglycerides are associated with human adipose tissue DNA methylation of genes linked to metabolic disease. *Human Molecular Genetics, 32*(11), 1875–1887. DOI: 10.1093/hmg/ddad024
55. Eckel, N., Li, Y., Kuxhaus, O., Stefan, N., Hu, F. B., & Schulze, M. B. (2018). Transition from metabolic healthy to unhealthy phenotypes an association with cardiovascular disease risk across BMI categories in 90257 women (the Nurses' Health Study): 30-year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol, 6*(9), 714–724. DOI: 10.1016/S2213-8587(18)30137-2
56. Abshirini, M., Mahaki, B., Bagheri, F., Siassi, F., Koohdani, F., Qorbani, M., Yavari, P., & Sotoudeh, G. (2020). Dietary fat quality and pre-diabetes: A case control study. *Int J Prev Med*, 11,160. DOI: 10.4103/ijpvm.IJPVM_243_18
57. Thanarajah, S. E., DiFeliceantonio, A. G., Albus, K., Kuzmanovic, B., Rigoux, L., Iglesias, S., Hanßen, R., Schlamann, M., Cornely, O. A., Brüning, J. C., Tittgemeyer, M., Small, D. M. (2023). Habitual daily intake of a sweet and fatty snack modulates reward processing in humans. *Cell Metab, 35*(4), 571–584.e6. DOI: 10.1016/j.cmet.2023.02.015
58. Worthmann, A., Ridder, J., Piel, S. Y. L., Evangelakos, I., Musfeldt, M., Voß, H., O'Farrell, M., Fischer, A. W., Adak, S., Sundd, M., Siffeti, H., Haumann, F., Kloth, K., Bierhals, T., Heine, M., Pertzborn, P., Pauly, M., Scholz, J. J., Kundu, S… Schlein, C. (2024). Fatty acid synthesis suppresses dietary polyunsaturared fatty acid use. *Nature communications, 15*(1), 45. DOI: 10.1038/s41467-023-44364-y
59. Sun, Y., Rong, S., Liu, B., Du, Y., Wu, Y., Chen, L., Xiao, Q., Snetselaar, L., Wallace, R., & Bao, W. (2023). Meal skipping and shorter meal intervals are associated with increased risks of all-cause and cardiovascular disease mortality among US adults. *Journal of the Academy of Nutrition and Dietetics, 123*(3), 417–423. DOI: 10.1016/j.jand.2022.08.119
60. Bruls, Y. M., de Ligt, M., Lindeboom, L., Phielix, E., Havekes, B., Schaart, G., Kornips, E., Wildberger, J. E., Hesselink, M. K., Muoio, D., Schrauwen, P., & Schrauwen-Hinderling, V. B. (2019). Carnitine supplementation improves metabolic flexibility and skeletal muscle acetylcarnitine formation in volunteers with impaired glucose tolerance: A randomized control trial. *EBio Medicine*, 49, 318–330. DOI: 10.1016/j.ebiom.2019.10.017
61. Nguyen, D., Samson, S. L., Reddy, V. T., Gonzalez, E. V., & Sekhar, R. V. (2013). Impaired mitochondrial fatty acid oxidation and insulin resistance in Aging: Novel protective role of glutathione. *Aging Cell, 12*(3), 415–425. DOI: 10.1111/acel.12073
62. Indarto, D., Rochmah, D. N., Wiboworini, B., Pratama, Y. M., & Wibowo, Y. C. (2022). Effects of vegetable consumption before carbohydrates on blood glucose and GLP-1-Levels among diabetic patients in Indonesia. *Int Prev Med, 13*(144), 36618536. DOI: 10.4103/ijpvm.IJPVM_704_20
63. Rasmussen, B. B., Holmbäck, U. C., Volpi, E., Morio-Liondore, B., Paddon-Jones, D., & Wolfe, R. R. (2002). Malonyl coenzyme A and the regulation of functional carnitine palmitoyltransferase-1 activity and fat oxidation in human skeletal muscle. *J Clin Invest, 110*(11), 1687–93. DOI: 10.1172/JCI15715
64. Sarabhai, T., Koliaki, C., Mastrototaro, L., Kahl, S., Pesta, D., Apostolopoulou, M., Wolkersdorfer, M., Bönner, A. C., Bobrov, P., Markgraf, D. F., Herder, C., & Roden, M. (2022). Dietary palmitate and oleate differently modulate insulin sensitivity in human skeletal muscle. *Diabetologia, 65*(2), 301–314. DOI: 10.1007/s00125-021-05596-z

65. Errazuriz, I., Dube, S., Slama, M., Visentin, R., Nayar, S., O'Connor, H., Cobelli, C., Das, S. K., Basu, A., Kremers, W. K., Port, J., & Basu, R. (2017).Randomized Controlled Trial of a MUFA or Fiber rich diet on hepatic fat in Prediabetes. *The Journal of Clinical Endocrinology & Metabolism, 102*(5), 1765-1774. DOI: 10.1210/jc.2016-3722
66. Seidelmann, S., Claggett, B., Cheng, S., Henglin, M., Shah, A., Steffen, L. M., Folsom, A. R., Rimm, E. B., Willett, W. C., & Solomon, S. D. (2018). Dietary carbohydrate intake and mortality: A prospective cohort study and meta-analysis. *Lancet Public Health, 3*(9), e419 – e428. DOI: 10.1016/S2468-2667(18)30135-X
67. Alrashed, F., Sindhu, S., Al Madhoun, A., Bahman, F., AlSaeed, H., Akhter, N., Malik, M. Z., Alzaid, F., Al-Mulla, F., & Ahmad, R. (2023). Low carbohydrate intake correlates with trends of insulin resistance and metabolic acidosis in healthy lean individuals. *Front. Public Health*, 11, 1115333. DOI: 10.3389/fpubh.2023.1115333
68. Costabile, G., Della Pepa, G., Salamone, D., Luongo, D., Naviglio, D., Brancato, V., Cavaliere, C., Salvatore, M., Cipriano, P., Vitale, M., Corrado, A., Rivellese, A. A., Annuzzi, G., & Bozzetto, L. (2022). Reduction of de novo lipogenesis mediates beneficial effects of isoenergetic diets on fatty liver: Mechanistic insights from the MEDEA randomized clinical trial. *Nutrients, 14*(10), 2178. DOI: 10.3390/nu14102178
69. Clamp, L. D., Hume, D. J., Lambert, E. V., & Kroff, J. (2017). Enhanced insulin sensitivity in successful, long-term weight loss maintainers compared with matched controls with no weight loss history. *Nutr Diabetes, 7*(6), e282. DOI: 10.1038/nutd.2017.31
70. Cistola, D. & Dwivedi, A. K. (2022). Overweight is not a diabetes risk factor for insulin-sensitive individuals: CARDIA 30-year follow up. *Metabolism*, 128, 155095. DOI: http://dx.doi.org/10.1016/j.metabol.2021.155095
71. De Oliveira C. M., Pavani, J., Liu, C., de Oliveira Alvim, R., Balcells, M., Mourão-Junior, C. A., Krieger, J. E., da Costa Pereira, A. (2020). Trigylceride glucose Index as a tool to motivate early lifestyle modification in young adults at diabetes risk: The Baependi Heart Study. *Preventive Medicine Reports*, 20, 101172. DOI: 10.1016/j.pmedr.2020.101172
72. Sanchez-Escudero, V., García Lacalle, C., González Vergaz, A., Remedios Mateo, L., Marqués Cabrero, A. (2021). The triglyceride/glucose index as an insulin resistance marker in the pediatric population and its relation to eating habits and physical activity. *Endocrinol Diabetes Nutr (Engl Ed), 68*(5), 296-303. DOI: 10.1016/j.endinu.2020.08.008
73. Murata, S., Ebeling, M., Meyer, A. C., Schmidt-Mende, K., Hammar, N., & Modig, K. (2024). Blood biomarker profiles and exceptional longevity: Comparison of centenarians and non-centenarians in a 35 year follow-up of the Swedish AMORIS cohort. *GeroScience, 46*(2), 1693–1702. DOI: 10.1007/s11357-023-00936-w
74. Araújo, J., Cai, J., & Stevens, J. (2019). Prevalence of optimal metabolic health in American adults: National Health and Nutrition Examination Survey 2009–2016. *Metab Syndr Relat Disord, 17*(1), 46–52. DOI: 10.1089/met.2018.0105
75. Hall, E., Jönsson, J., Ofori, J. K., Volkov, P., Perfilyev, A., Dekker Nitert, M., Eliasson, L., Ling, C., & Bacos, K. (2019). Glucolipotoxicity alters insulin secretion via epigenetic changes in human islets. *Diabetes, 68*(10), 1965–1974. DOI: 10.2337/db18-0900
76. Ramos, E. L. L., Lima, M. F. C., Azevedo, A. C. S. F., Lopes, M. G. F., Moreira, A. P. B., & Souza, C. T. (2023). Effects of diets rich in monounsaturated fatty acids on the management and prevention of insulin resistance: A systematic review. *Grasas y Aceites, 74*(3). DOI: https://doi.org/10.3989/gya.1125212
77. Tian, S., Lei, Y., Zhao, F., Che, J., Wu, Y., Eun Kang, Y., & Shan, Y. (2024). Improving insulin resistance by sulforaphane via activating Bacteroides & Lactobacillus-SCFAs-GPR-GLP1 signal axis food funct. DOI: https://doi.org/10.1039/D4FO01059K