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Hepatic-Metabolite-Based Intermittent Fasting Enables a Sustained Reduction in Insulin Resistance in Type 2 Diabetes and Metabolic Syndrome

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ABSTRACT

Insulin resistance is the hallmark of Type 2 Diabetes and is still an unmet medical need. Insulin resistance lies at the crossroads of non-alcoholic fatty liver disease, obesity, weight loss and exercise resistance, heart disease, stroke, depression, and brain health. Insulin resistance is purely nutrition related, with a typical molecular disease food intake pattern. The insulin resistant state is accessible by TyG as the appropriate surrogate marker, which is found to lead the personalized molecular hepatic nutrition system for highly efficient insulin resistance remission. Treating insulin resistance with a molecular nutrition-centered approach shifts the treatment paradigm of Type 2 Diabetes from management to cure. This allows remission within five months, with a high efficiency rate of 85 %. With molecular intermittent fasting a very efficient treatment for prediabetes and metabolic syndrome is possible, improving the non-alcoholic fatty liver disease (NAFL) state and enabling the body to lose weight in a sustainable manner.

Introduction

Today, treatment of Type 2 Diabetes is glucose-centered and symptom-oriented. The history of most patients with Type 2 Diabetes is a gradual rise in blood glucose concentrations over time, despite medication, as reported by Madsen et al. [1]. Insulin resistance is the hallmark of Type 2 Diabetes, but is still an unmet medical need even though advances in diabetes medicines have been made over the last several years. Ferrannini et al. [2] reported that the same is true for the fast and simple detection of insulin resistance. Insulin resistance lies at the key crossroads of metabolic and mitochondrial dysfunction, visceral fat, non-alcoholic fatty liver (NAFL), muscle exercise and weight loss resistance, subclinical inflammation, metabolic syndrome (MetS), overweight, and obesity, and is characterized by epigenetically driven accelerated aging, as Nannini et al. [3] reported. Insulin resistance plays a key role in a reduced capability of the immune system to kill pathogens such as viruses and bacteria, as De Rosa et al. [4] and Chávez-Reyes et al. [5] reported. Vestergaard Jensen et al. [6] reported insulin resistance as an important risk factor for community-acquired pneumonia. Insulin resistance predisposes to cardiovascular disease and shortens human lifespan, as data from Gardner et al. [7] showed. Insulin resistance is reported to drive other major non-communicable diseases, such as high blood pressure, chronic kidney disease (Chen et al. [8]), depression (Won Lee et al. [9]; Geraets et al. [10], Ford et al. [12]), and stroke (Rundek et al. [11]). Alzheimer's disease and dementia are also highly correlated to increased levels of triglycerides at midlife as data from Nägga et al. [13] showed. Insulin resistance also underlies many obesity-related cancer developments, as reported by Sung et al. [14].

Insulin resistance is independently correlated with increased risk of incident diabetes in Chinese adults, as reported by Li et al. [15], and is closely related with higher mortality for COVID-19, according to data reported by Ren et al. [16]. Diabetes is the most important cause of mortality in COVID-19 hospitalized patients, as reported by Corona et al. [17]. A large-scale analysis reported by McGovern et al. [18] found that the COVID-19 mortality risk increases in patients with Type 2 Diabetes due to drastic biological age acceleration. The prevalence of Type 2 Diabetes in Switzerland is estimated to be between 5.7 and 7.0%. Two-thirds of patients with Type 2 Diabetes are aware of their status, and over three-quarters of those who are aware are treated, according to data from Kaiser et al. [19]. In the US, adults with optimal metabolic health are a small percentage of the population: 17.6%, according to Araujo et al. [20].

Type 2 Diabetes is observed to correlate with obesity regardless of the genetic risks. The currently available obesity-oriented treatment options for Type 2 Diabetes are either a bariatric operation, or a caloric weight-loss strategy that involves a very low-calorie diet, as reported by Kerr et al. [21], Willi et al. [22], and Xin et al. [23]. As observed by Baskota et al. [24], a bariatric operation can only be proposed for those with a BMI > 30 and should not be proposes for non-diabetic obese patients.

BMI is not the main driver for insulin resistance; insulin resistance drives BMI

Diabetes primarily depends on visceral fat and not BMI, according to data from Vistisen et al. [25]. Her group found that the great majority of patients who had modest weight gains before diagnosis had the highest diabetes risk. Wu et al. [26] reported that, in Mexican Americans, metabolic health has a greater impact on diabetes than overweight/obesity. Eckel et al. [27] reported that the quality of metabolic health was decisive for diabetes progression, irrespective of BMI. Acquired obesity independent of genetic risk is primarily related to deleterious alterations in the lipid metabolism, per data found by Pitiläinen et al. [28] in studies of twins. Insulin resistance discriminates between healthy and unhealthy phenotypes of obesity and leanness, as reported by Owei et al. [29] and Mongraw-Chaffin et al. [30] and drives the unhealthy obese phenotype into developing Type 2 Diabetes.

Insulin resistance has its root not only in disturbed glucose metabolism but also in a derailed fatty acid metabolism leading to glucolipotoxic conditions and beta-cell death, as reported by Bagnati et al. [31]. Increased blood triglycerides accompanied by lower HDL values represent an insulin resistant metabolic status and are purely nutrition-related. Triglyceride levels showed a significant negative correlation with BMI and body fat. HDL cholesterol was significantly negatively correlated with waist circumference and positively correlated with body fat, as data from Telles et al. [32] showed.

Lipid indices, which can be easily calculated with routine laboratory tests, may be useful markers for insulin resistance risk assessments in clinical settings, according to Lee et al. [33]. The triglyceride to HDL ratio allow identification of the insulin-resistant metabolic state, and a high TG:HDL-C ratio at baseline may be a useful surrogate indicator of future Type 2 Diabetes, as reported by Lim et al. [34]. The TyG index, calculated based on fasting triglyceride and glucose blood values, correlates highly with insulin resistance. Both markers, the TG:HDL-C and TyG present a significant association with lifetime cardiovascular risks in adults reported by Rojas-Humpire et al. [35] and Si et al. [36]. The TyG index correlated highly with the epigenetic age acceleration, as data from Arpon et al. [37] showed. HOMA-IR had a significant positive correlation with the TyG and TG:HDL indices, as reported by Çin et al. [38] and Kron et al. [39].

Triglycerides are endogenously formed after an excess of glucose ingestion via a de novo lipogenesis pathway forming malonyl-CoA, diacylglycerols, and palmitic acid (16:0), and directly influence insulin resistance, as Lyu et al. [40] reported. Lee [41] reported palmitic acid 16:0 was positively associated with incident heart failure in older adults. Malonyl-CoA is a master regulator for insulin sensitivity. Hyperglycemia with hyperinsulinemia increases malonyl-CoA production and inhibits functional CPT1 activity, while and shunting long-chain fatty acids away from oxidation and towards storage in human muscle, as reported by Rasmussen et al. [42]. Malonyl-CoA is the first reaction step for the de novo lipogenesis of palmitic acid, which is positively associated with Type 2 Diabetes, as data from Imamura et al. [43] showed. But de novo lipogenesis is also positively associated with saturated fatty acid intake and is elevated in patients with non-alcoholic fatty liver and Type 2 Diabetes, as reported by Imamura et al. [43]. The TyG index is significantly associated with incident NAFL, as reported by Kitae et al. [44] and Jimenez-Rivera et al. [45]. Kolb et al. [46] reported detrimental consequences of prolonged high insulin concentrations and argues for a lifestyle that limits circadian insulin levels. Skipping

breakfast a few times a week was associated with general adiposity and with general and central adiposity, as reported by Wadolowska et al. [47], and was also associated with a higher risk of insulin resistance, as data from Joo et al. [48] showed. Consuming a three-meal diet with a carbohydrate-rich breakfast allows insulin dose reduction, leading to weight loss and better glycemic control compared with an isocaloric six-meal diet, as reported by Jakubowicz et al. [49].

Food choices for a molecular dietary pattern developing an insulin-resistant metabolic state

Compared to normal glycemic adults, adults with Type 2 Diabetes make different food choices, favoring a high saturated fat diet with higher total fat and protein and less fiber, as reported by Breen et al. [50]. Increased insulin resistance favors continued unhealthy food choices via aberrant central insulin action, as reported by Tiedemann et al. [51], leading to a vicious cycle in which insulin resistance drives changes in taste perception, as observed by Pugnaloni et al. [52], leading to continued eating and snacking behavior. Saturated fat increases intramuscular triglycerides, and a decreased intake of saturated fatty acids could be beneficial in reducing intramuscular triglycerides and the associated risk of diabetes, according to data from Luukkonen et al. [53]. In obese subjects with normal glycemia, elevated circulating levels of free fatty acids during fasting is the major metabolic derangement candidate driving fasting hyperinsulinemia as a homeostatic response, as reported by Fryk et al. [54].

Maintaining glycemic control via a healthy fatty acid metabolism may be an emerging key factor for maintaining a healthy beta-cell formation for a normal glucagon metabolism, as reported by Grubelnik et al. [55]. Lower fiber intake of all types is associated with higher insulin levels. Triglyceride concentrations are potentially sensitive to fiber consumption, as reported by Hannon et al. [56]. Fiber intake at recommended levels may be associated with significant cardiometabolic benefits, as data from Dong et al. [57] showed. Higher intakes of dietary choline and betaine are associated with lower insulin resistance in the general population, as reported by Gao et al. [58].

The amount of dietary intake of animal protein was positively related to HOMA-IR, while plant protein was not significantly related to insulin resistance, as reported by Azemati et al. [59]. Plant-based proteins with polyphenols are reported by Meir et al. [60] and Castro-Barquero et al. [61] to improve HDL cholesterol and to have an inverse relationship with triglycerides. McKaye et al. [62] reported that a low intake of vitamin D, folate, magnesium, and potassium have a negative relationship to BMI, while other micronutrients, such as vitamins B12 and E, do not.

A personalized molecular feeding and control strategy for the remission of insulin resistance

The molecular dietary pattern of humans is directly related to transcriptions generating epigenetically the enzymatic pattern needed for a healthy metabolism for maintaining energy homeostasis. An unhealthy dietary pattern leads via the epigenetically driven transcription to an unfavorable enzymatic pattern, leading to insulin resistance to rescue the energy homeostasis, as reported by Hall et al. [63].

The CPT1 gene expression is epigenetically silenced in the unhealthy obese phenotype, as data from Maples et al. [64] show. The β-oxidation genes are also downregulated during weight loss, preserving metabolic inflexibility. Metabolic flexibility is lacking at the extreme of the metabolic phenotype in obese youth with dysglycemia related to a defect in insulin sensitivity, limiting substrate utilization, as reported by Bacha et al. [65]. An epigenomic study by Irvin et al. [66] and Mamtani et al. [67] found that the CPT1 locus influenced by methylation is strongly and robustly associated with low-density lipoprotein cholesterol, triglycerides, as well as visceral fat and waist circumference. Lai et al. [68] found that the proportion of total energy supplied by carbohydrates and fat can have a causal effect on the risk of metabolic diseases, via the epigenetic status of the CPT1A gene directly influencing metabolic health through CPT1A gene activation or silencing. Epigenetic signatures are associated with dyslipidemia and are strongly associated with HOMA-IR, as a direct measure for insulin resistance. HOMA-IR values ≤ 3 as the threshold for Type 2 Diabetes showed a different methylation pattern than for individuals with HOMA-IR > 3, as reported by Arpon et al. [69].

Below we present a precisely designed and personalized molecular feeding strategy, integrating food research findings, and combining an epigenetic view aimed at the TyG and TG:HDL indices, for simple metabolic steering and control, for efficient insulin resistance normalization.

Compliance with ethical standards

Ethical approval: All patients were treated following an ethical approach to select the optimal treatment procedure according to their medical needs and the patients agreed before therapy began to possible reduction of their medications, when necessary.

Informed consent: Patient data and information have been completely anonymized.

Materials and Methods

A personalized nutritional method for insulin resistance and diabetes remission

Hepatic intermittent fasting therapy consists of two parts, always with a three meal per day diet. The first part is a very low calorie diet (VLCD) to reverse Type 2 Diabetes. The VLCD is followed by a personalized, hepatic-focused whole food diet, epigenetically oriented to stabilizing the metabolism that was reprogrammed in the VLCD part. Both parts, VLCD followed by the whole food diet, are used for diabetes remission therapy. The VLCD combines protein shakes (Protiline) with selected vegetable intake focused mainly on sulforaphane, betaine, and choline. The personalized, hepatic-focused whole food diet is applied for the normalization of MetS and prediabetes. The whole food diet 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 [70].

The key molecules related to insulin resistance of the food are digitally calculated for molecular control. The healthy range of molecular concentration of the key food ingredients is estimated and visualized for the client for easy self-control, using the "EPIKonzept App." The client can simply follow daily his food selection and is informed about how well he is achieving on a molecular 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 parts of the therapy, VLCD and a personalized whole food diet, are supported with tailored biochemically active product formulas, namely EPIGENOSAN and METHYLOSAN.

Epigenosan is a tableted 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 [71].

Epimethylosan is a capsuled formula product based on broccoli sprouts and white asparagus 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

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) × fasting glucose (mg/dl)/2], as published by Simental-Mendia et al. [72]. 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. [73].

For the nutritional analysis, the DGExpert program was used.

The liver index was calculated according to the formula liver index:

$$(e^{0.953 \, * \, \log e \, (triglycerides) \, + \, 0.139 \, * \, BMI \, + \, 0.718 \, * \, \log e \, (ggt) \, + \, 0.053 \, * \, waist \, circumference - 15.745})/(1 + e^{0.953 \, * \, \log e \, (triglycerides) \, + \, 0.139 \, * \, BMI \, + \, 0.718 \, * \, \log e \, (ggt) \, + \, 0.053 \, * \, waist \, circumference - 15.745}) \times 100$$

according to Bedogni et al. [74].

Diabetes remission group

The Type 2 Diabetes group consisted of 13 patients (▶ Table 1). The inclusion criteria for the diabetes remission group were to be not older than 70 years old; 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 ≥ 25. Diabetes remission was defined as glycated haemoglobin (HbA$_{1c}$) of less than 47.5 mmol/mol (< 6.5 %) and fasting glucose of less than 7.0 mmol/l after at least 2 month off all antidiabetic medications.

MetS/prediabetic therapy group

The MetS group consisted of 21 patients (▶ Table 2). The inclusion criteria for the MetS/prediabetic group were no depressive disorders at the time of application; and BMI ≥ 20 kg/m^2.

▶ **Table 1** Diabetes remission group participants overview.

Patient	BMI initially	BMI after 60 d	BMI after 150 d	Sex	Age	Antidiabetic medication	Years diagnosed
Diab 1	33.3	29.2	29.2	F	55	Metfin	5
Diab 2	34.3	31.2	25.9	F	62	Metformin	1
Diab 3	26.8	22.2	21.3	M	54	Glavumet	2
Diab 4	32.8	27.3	26.1	M	55	None	<1
Diab 5	31.4	26.5	24.6	F	56	Metfin	7
Diab 6	31.5	27.1	25.2	M	47	Metfin	3
Diab 7	35.9	29.4	26.7	M	46	Metfin	4
Diab 8	26.8	24.5	22.6	F	47	None	<1
Diab 9	26.8	24.4	22.0	M	64	Metfin	Unknown
Diab 10	33.3	26.5	26.7	M	61	None	Unknown
Diab 11	54.3	47.6	46.5	M	50	Janumet	2
Diab 12	38.9	36.0	29.7	F	68	Januvia	2
Diab 13	41.8	36.2	31.1	F	35	None	<1
Mean BMI	34.4	29.9	27.5				

▶ **Table 2** MetS/prediabetic group participant overview.

Patient	Age	Sex	Medication	BMI initially	BMI after Therapy (150 d)	Initial metabolic status
MetS 1	47	w	None	33.2	29.3	Severe risk for insulin resistance
MetS 2	60	m	None	37.2	32.5	Severe risk for insulin resistance
MetS 3	49	w	Antiepileptics	31.9	30.7	Severe risk for insulin resistance
MetS 4	70	w	None	31.4	26.1	Insulin resistant
MetS 5	71	m	None	26.5	22.9	Insulin resistant
MetS 6	84	w	None	27.8	26.2	Prediabetic
MetS 7	82	w	Statin	39.6	36.1	Prediabetic
MetS 8	51	w	None	23.0	20.7	Insulin resistant
MetS 9	53	m	None	33.6	29.1	Prediabetic
MetS 10	32	w	None	24.6	21.3	Insulin resistant
MetS 11	66	m	None	32.1	29.1	Insulin resistant
MetS 12	63	m	Statin	30.4	27.0	Prediabetic
MetS 13	69	m	Statin	37.5	33.6	Severe risk for insulin resistance
MetS 14	76	m	None	22.9	22.2	Prediabetic
MetS 15	79	w	None	26.9	25.5	Insulin resistant
MetS 16	60	w	None	32.7	28.8	Insulin resistant
MetS 17	56	m	Antidepressive	32.8	28.1	Prediabetic
MetS 18	57	m	None	31.4	25.4	Insulin resistant
MetS 19	49	m	None	26.9	23.8	Insulin resistant
MetS 20	70	m	None	38.8	34.2	Insulin resistant
MetS 21	43	w	Statin	36.9	32.0	Insulin resistant
Mean BMI				31.3	27.8	

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 dietary pattern of MetS, prediabetes and Type 2 Diabetes patients observed

The macromolecular dietary pattern of patients with MetS, prediabetes, or Type 2 Diabetes of both patient groups who had an initial TyG value higher than baseline shows a similar initial pathological nutritional pattern irrespective of BMI. An average intake of saturated fats of 35 % and unsaturated fats of 46 %; an average glucose intake of 82 g/d, and an average fiber intake of 20 g/d was observed.

Type 2 Diabetes remission results

The hepatic intermittent fasting therapy delivered efficient results, reversing Type 2 Diabetes within 60 days for all participants as measured by fasting glucose (▶ **Fig. 1**). Antidiabetic medications could be omitted for all patients at the latest at day 60 of the VLCD part of the therapy. The reprogrammed metabolism in these 60 days was stabilized during the personalized whole food nutrition part of the therapy up to 150 days, as shown in ▶ **Fig. 1**. All patients could avoid their antidiabetic medications during the 90 days of the personalized whole food phase, and the diabetes remission rate was estimated to be 85 %, according to HbA_{1c} and fasting glucose levels.

Adjuvant Type 2 Diabetes therapy results for uncontrolled diabetes

▶ **Table 4** shows results achieved in a patient with uncontrolled diabetes.

MetS, NAFL, and prediabetes therapy results

In the MetS group, 21 patients were insulin resistant according to the TyG index value, and six were prediabetic. The duration of the therapy needed to reprogram the metabolisms of all patients in the MetS group and get them stably out of the diseased path was up to 150 days (▶ **Fig. 2**). The method shows fast results within 30 to 50 days.

Discussion and Conclusions

The paradox of satiety and nutrient hunger irrespective of BMI

A similar macro- and micromolecular dietary pattern observed for MetS, prediabetes, or Type 2 Diabetes patients with too high intake
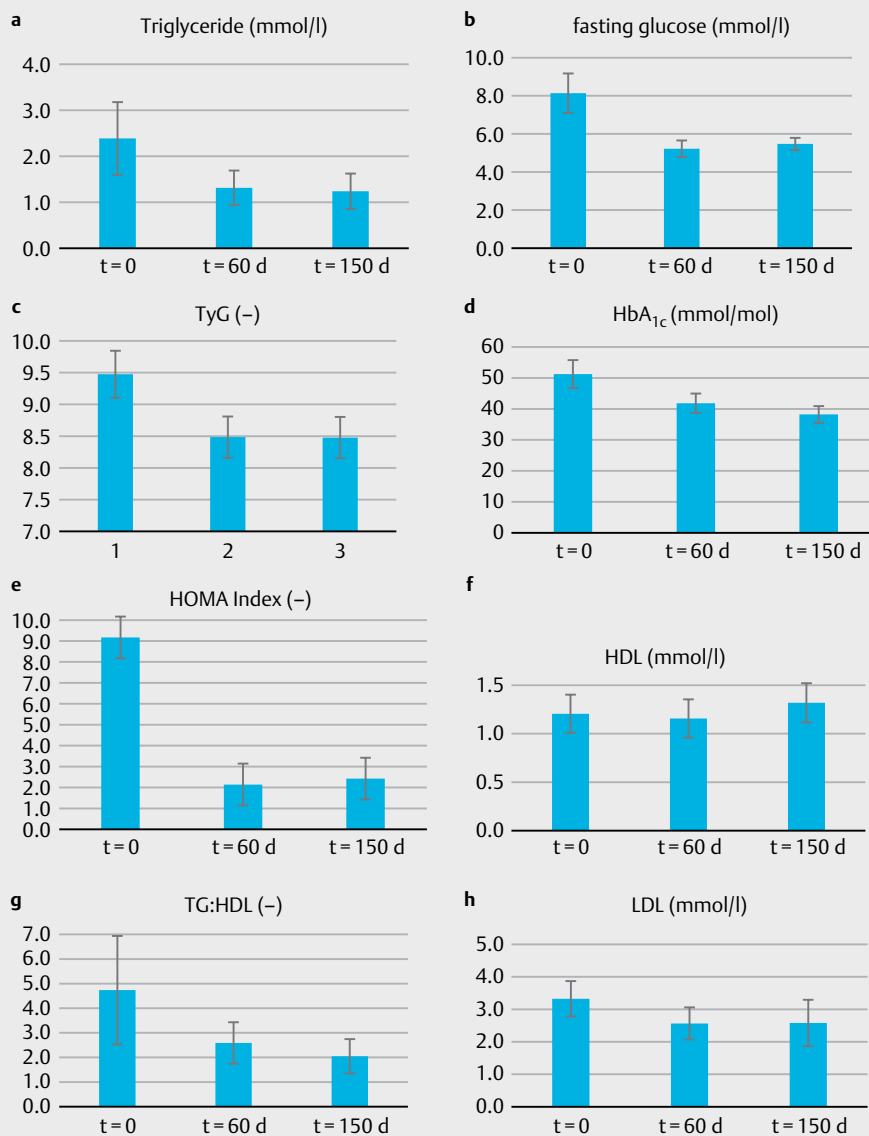
▶ **Fig. 1** Median results of the diabetic remission group (n = 13) at three points in time: start (t = 0), after 60 days of VLCD, and after 150 days with the personalized whole food application. The single lead parameters and the corresponding surrogate biomarkers TyG and TG:HDL, as the leading medical indices for nutritional health, are shown. All data with p < 0.001, confidence interval 95 %. **a** Triglycerides, threshold value 1.7 mmol/l; **b** fasting glucose, threshold value 5.6 mmol/l for normal value, threshold value for diabetes remission < 7.0 mmol/l; **c** TyG, calculated from a and b, threshold value 8.73; **d** HbA$_{1c}$, threshold value for diabetes < 47.54 mmol/mol; **e** HOMA Index, threshold value for Type 2 Diabetes > 3; **f** HDL values, threshold value > 1.0 mmol/l; **g** TG:HDL ratio, threshold value for insulin resistance > 3.0; **h** LDL, threshold value 3.3 mmol/l. HbA$_{1c}$ and fasting glucose are the relevant Type 2 Diabetes remission parameters, as defined.

of saturated fats, unsaturated fats and glucose intake and a too low intake of fiber is in close agreement as reported by Breen et al. [50]. At the outset, all participants also deviated from the RDA of micronutrients magnesium, potassium, and vitamin D, as also reported by McKaye [63]. This may point to a new paradox for insulin-resistant risks, showing an abundance of glucose and palmitic acid intake, a shortage in unsaturated fat intake, and a scarcity for micronutrients, irrespective of BMI. No strong correlation with a typical macromolecular nor micromolecular dietary pattern could be extracted concerning the severity of the insulin resistance, nor BMI nor waist circumference. But a molecular nutrition deviation irrespective of BMI leading to insulin resistance is particular congruent with nutritional stress for hypertriglyceridemia, hyperinsulinemia and low HDL-cholesterol. As a consequence a combination of TyG and TG:HDL as lead biomarkers for leading the food intake to structure the personalized program for optimal diabetes remission was chosen.

Type 2 Diabetes remission is not driven by calories only

TyG as the lead surrogate biomarker for nutritional feeding allows structuring personalized whole food nutrition for diabetes remis-

sion for all BMI categories (≥25), and a nutritional structure that is not just focused on calories (as is the main approach in today's marketplace). Caloric aspects are taken into account of the personalization algorithm of the diet, but calories are not the leading factor only and are calculated according to the body's energy needs. For Patient 8 (▶ Table 1) this is shown in detail (▶ Table 3). Patient 8 presented a starting BMI of 26.8. The patient's diet before therapy, with a high intake of saturated fats and glucose, and low fiber intake with a typical in-between snacking behavior, showed similar calorie intake (isocaloric) and macronutrient distribution to her diet after the therapy (▶ Table 3).

▶ Table 3 BMI is not the driver for Type 2 Diabetes remission. Isocaloric nutrition of a patient before and at the end of therapy, no medication, <1-year diagnosis, female, 47 years, initial BMI 26.8.

Isocaloric nutrition, composition	Before therapy	After therapy
Total calories kcal/day	1676	1560
Carbohydrate g/d	188	160
Carbohydrate kcal/d	771	656
% carbohydrate of total calorie intake	53	54
Proteins g/d	80	83
Proteins as kcal/d	330	338
% protein of total calorie intake	20	22
Total fat g/d	66	63
Fat as kcal/d	611	590
% of total fat intake	36	38
Saturated fat g/d	27.6	12.5
Monounsaturated fat g/d	21.6	28.2
Polyunsaturated fat g/d	8.6	17.6
Omega-3 fatty acids g/d	0.8	3.3
Fiber g/d	26.7	44.9
% fiber of total calorie intake	6.5	11.8
Vitamin D µg/day	1.3	9.2
Magnesium mg/day	279.0	577.0
Potassium g/d	2.4	4.3
Fasting blood values/ anthropometric data	Before therapy	After therapy
Triglyceride mmol/l	2.7	1.4
HDL mmol/l	1.2	1.3
LDL mmol/l	3.9	3.1
Glucose mmol/l	9.1	5.4
HbA$_{1c}$ mmol/mol	50.8	38.8
HOMA	8.5	2.7
TyG	9.9	8.7
TG:HDL	5.1	2.4
BMI kg/m^2	26.8	22.6
Waist circumference cm	97.0	90.0

As can be seen, the molecular distribution of the fatty acid fraction was completely changed after therapy. After therapy, saturated fat intake values were normal (<13 g); intake of fiber was above the recommended value of 40 g/d; and vitamin D, magnesium, and potassium all reached values above the RDA. The HOMA index continued to improve after the end of the therapy (after 150 days) and was estimated to be 1.57 after 323 days.

Personalized molecular nutrition for Type 2 Diabetes remission

A highly efficient and effective insulin resistance remission result was achieved for all patients across all BMI categories, according to the lead biomarker: 85% of the patients (11 out of 13) achieved remission, and only one patient did not reach the lower threshold value of the TG:HDL ratio of 3.0. The TG:HDL ratio combined with TyG are the leading biomarkers but are weighted more to stabilizing the metabolism reprogramming that occurs during the VLCD part of the therapy. Our finding confirmed Achilike et al. [75], who found that TG:HDL has the power to produce a metabolically healthy phenotype. The personalized nutritional strategy reduces the triglyceride levels, and the molecular personalized whole food diet reduces the buildup of new triglycerides, leading to a negative balance that reaches normal levels over time. It is of utmost importance to keep the triglyceride buildup under control since triglycerides can cross the blood-brain barrier and contribute to decreased satiety, as reported by Banks et al. [76].

Improvements in triglycerides were very fast during VLCD, averaging 48%. The fasting glucose adaptation during VLCD was also very fast, and all patients reached the threshold value <7 mmol/l within the first 14 days.

Ten patients reached fasting glucose values <5.6 mmol/l, and all patients were better than 6.3 mmol/l after completing the therapy (150 days). On average, fasting glucose values improved by 33% (2.66 mmol/l).

Diabetes remission was always accompanied by weight loss as a symptomatic effect of the metabolic improvements. Kelly et al. [77] reported a mean diabetes remission rate of 49.4% applying very low calorie diets. The VLCD part of the intermittent hepatic therapy, which is focused on the cause of insulin resistance, delivers more effective results, as our reported data show (▶ Fig. 1).

The weight loss reached was not homogenous, since the initial BMI was not, and the therapy approach is not focused on calories only. The statistical significance and regression coefficient for diabetes reversion against the HOMA Index was highest for the TyG Index (0.61, p < 0.001), compared to the TG:HDL Index (0.41, p < 0.05). The weight loss achieved also showed a lower regression correlation to the HOMA Index (0.43, p < 0.05). This implies that the TyG index is the key biomarker for diabetes remission, with a strong focus on triglyceride normalization as a key success factor. This does reflect the current research that triglycerides are driving hyperinsulinemic conditions that disturb the glucose metabolism, leading to weight increase as a homeostatic defending mechanism.

The HOMA Index as a medically accepted analytical value for insulin resistance was always surpassed, and on average was reduced by 79%, or 6.7 units over the entire therapy length. For one hyperinsulinemia patient, an improvement in the HOMA Index of 12 times was observed. All patients reached the <3 threshold point of

▶ **Table 4** Time course of a Type 2 Diabetes patient with uncontrolled diabetes (male, 55 years).

Analysis	Before	One month after	Norm value	Unit
Cholesterol	2.74[*]	2.4[*]	<5.2	mmol/l
HDL cholesterol	0.77	0.79	>1.0	mmol/l
LDL cholesterol	1.14[*]	1.21[*]	<3.3	mmol/l
Triglycerides	3.58[*]	1.55[*]	<1.7	mmol/l
Glucose	12.28[**]	5.77[**]	3.9–5.6	mmol/l
TyG	10.45	8.86	<8.73	–
ASAT/GOT	0.62	0.63	<0.85	µmol/s[*]l
ALAT/GPT	0.88	0.69	<0.85	µmol/s[*]l
GGT	1.24	1.05	<1.19	µmol/s[*]l
Cortisol	56	<28		nmol/l
Insulin (ip)	0.52	0.09	0.02–0.12	nmol/l
HOMA Index	39.2[**]	3.2[**]	<3	–
Waist circumference	115	109	<94	cm
BMI	31.6	29.4	20–25	kg/m^2
Bodyweight	99.8	92.9		kg

[*] Statins; [**] Antidiabetics.

the HOMA Index (3.8 reached for this patient, with a starting HOMA Index of 28). Over the full course of the therapy, a success rate of >90% could be estimated according to the HOMA Index. All patients of the diabetes group reached HbA$_{1c}$ values <47.54 mmol/mol, at the end of the 150 days time window. The average improvement in HbA$_{1c}$ was 17%, or 21.8 mmol/ml, which is higher than the 6.65 mmol/mol achieved in the caloric diabetes remission study reported by Ades et al. [78] that had a VLCD with a similar therapy duration of six months.

The importance of the triglyceride metabolism as presented is further supported by Ma et al. [79] and Lim et al. [80] who report that triglyceride levels are independently correlated with insulin resistance and islet beta-cell function in individuals with dyslipidemia.

We observed a relationship between the time required to achieve the threshold value of fasting glucose and the prior duration of Type 2 Diabetes and medication taken, but due to the limited number of patients this observation is in conclusive.

Adjuvant diabetes therapy to the uncontrolled medicated patient

Uncontrolled diabetes can be improved efficiently by restoring normal triglyceride levels, leading to normal insulin levels, by applying the personalized whole food part of the therapy (▶ **Table 4**).

The initial fasting glucose value of 12.28 mmol/l was reduced to 5.7 mmol/l in 30 days, while keeping the antidiabetic medication unchanged. Insulin resistance according to the HOMA Index was reduced by a factor of more than 10 (from 39.2 to 3.2), almost reaching the lower threshold value of 3.0 within 30 days of application. The TyG index estimated was 8.86 after application (threshold 8.73) and indicates improved status or almost no remaining in-

sulin resistance. The triglycerides level was reduced from 3.58 mmol/l to 1.55 mmol/l (but still taking statins). Cortisol was reduced from 56 to <28. The vicious cycle of increased cortisol paired with insulin resistance leading to hyperinsulinemia driving visceral fat was changed from a pathologic insulin level from 0.52 to a normal insulin level of 0.09 within 30 days of application.

Triglycerides have emerged as a new risk factor for cardiovascular disease in Type 2 Diabetes, as reported by Ye et al. [81]. According to Halldin et al. [82], the risk factor cholesterol has shifted more toward the risk factor triglycerides. Statins do not lower triglycerides adequately, as reported by Toth et al. [83] and, as reported by Shimoda et al. [84], the durability of the glucose-lowering effects from DPP-4 inhibitors can be better maintained if strict triglyceride management takes place.

Insulin resistance remission for MetS and prediabetes patients normalizing triglycerides

Normalization of MetS, prediabetes, and amelioration of NAFL is mediated by the reduction of triglycerides, similar to what is observed in Type 2 diabetes patients. The patients reported in their anamnesis a weight loss resistance which can be overcome with a fast normalization of the dyslipidemic state and triglyceride levels within the two first weeks of the personalized whole food part of the therapy. The molecular nutrition focused on the "one carbon" and CPT1 metabolism of the whole food part of the intermittent hepatic therapy delivers fast triglyceride amelioration. After 30 days of application of the personalized whole food intermittent fasting therapy part, the average TyG index was improved by 9%. Sixteen patients reached the lower threshold value <8.73 concerning insulin resistance but also TG:HDL <3. This corresponds to >76% efficiency for insulin resistance normalization respectively remission.
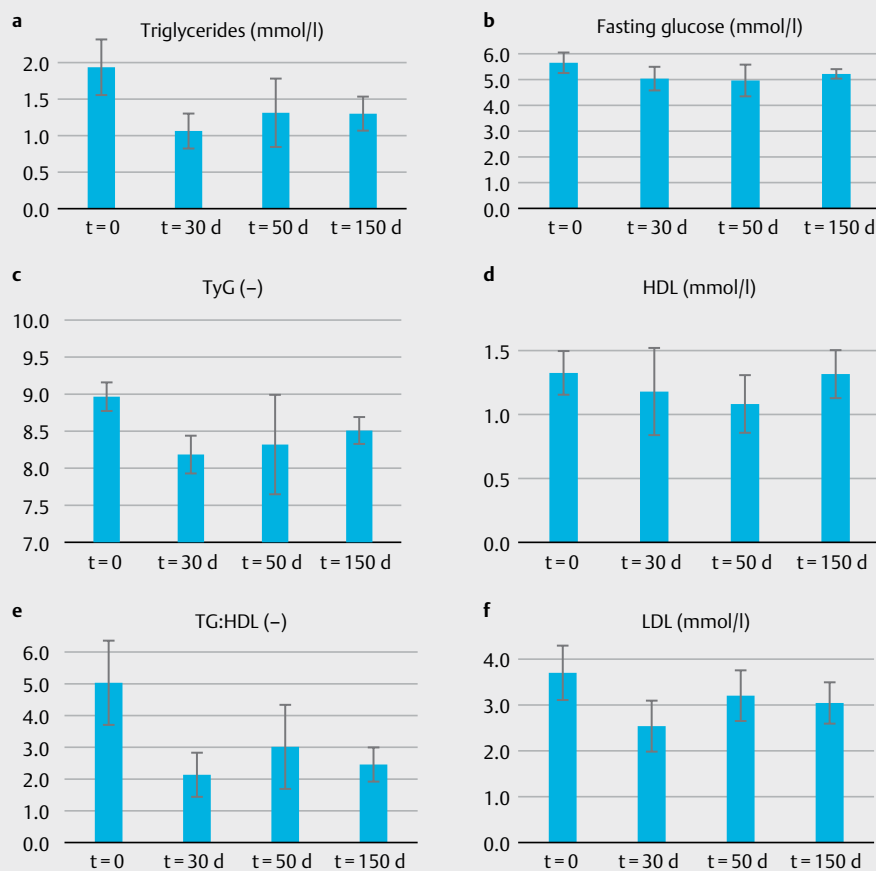
▶ **Fig. 2** Median results of the MetS/prediabetic group (n = 21) at four-time windows: start t = 0, at 30 days, at 50 days, and at 150 days. The single lead parameters and the corresponding surrogate biomarkers TyG and TG:HDL ratio as the leading medical index for nutritional health, are shown. All data with p < 0.001, confidence interval 95 % **a** Triglyceride course, threshold value 1.7 mmol/l; **b** fasting glucose course, threshold value 5.6 mmol/l for normal; **c** TyG course, calculated from **a** and **b**, threshold value 8.73; **d** HDL values, threshold value > 1.0 mmol/l; **e** TG:HDL ratio, threshold value for insulin resistance > 3.0; **f** LDL, threshold value 3.3 mmol/l.

Those five patients who were still slightly above the threshold showed good improvement but needed more time to reach the lower threshold. All initially prediabetic patients were no longer prediabetic after 150 days of application. The average improvement in triglyceride reduction was 33 % within 150 days. This is in accordance to Farell et al. [85] of key importance in breaking weight loss resistance, since early and established NAFL is responsible for this effect due to triglyceride accumulation. We measured an average improvement of the liver index within the first 50 days of 29 units. The initial median liver index was estimated as 81 units. According to Khan et al. [86], the modulation of triglycerides and insulin resistance represents a potential new strategy for NAFL treatment.

Triglyceride values stabilized after 50 days, HDL cholesterol increased, and LDL cholesterol decreased, stabilizing the metabolic and weight loss goals that had been reached.

Weight reduction occurred as a result of the metabolic improvement, with a mean BMI reduction of about 8 % within 50 days and up to 11 % within 150 days. To date, weight loss is the only existing therapy for NAFL according to Hydes et al. [87]. Our results suggest that, with a triglyceride and insulin resistance focus paired for weight loss, a new efficient NAFL treatment option is available.

As conclusion, the applied therapeutically method allows reversing the Type 2 Diabetic metabolism within 60 days and remission within 150 days with high efficiency. This shifts the treatment paradigm for Type 2 Diabetes from management to cure. Applying these method to patients with MetS and/or prediabetes can normalize their insulin resistance or prediabetes completely within 50 to 150 days. Our results favor a molecular nutritional diabetes prevention and remission strategy that is focused on triglyceride normalization with TyG as the lead biomarker, but that also combines a caloric approach enabling dietary molecular nutrition with an epigenetic point of view as a completely new diabetes prevention and remission strategy, and also a new treatment option for NAFL patients.

The pilot study has strengths and also weaknesses. Its major strength is the achievement of insulin resistance and Type 2 Diabetes remission in a significant, fast, and highly efficient way. The method is completely digitally supported for easy application and combines smart formulas of active ingredients to support the nutritional and metabolic adaptation. The presented method can establish a new treatment option that cures Type 2 Diabetes. The weakness of the pilot study is a limited number of persons and inhomogeneous patient characteristics.

Additional studies might be of interest from a scientific point of view, both to measure further data from more homogenous patient groups, and also to explore the epigenetic effects involved. However, from a practical and an application point of view, the methodology is very robust, proven, simply to apply, completely digitally supported, and ready to be used on a larger scale. Applying this new paradigm of a personalized molecular dietary pattern control for insulin resistance remission could revolutionize diabetes medicine and could also contribute beneficially to reduce the economic burden of Type 2 Diabetes and its related diseases.

Conflict of Interest

The authors declare that they have no conflict of interest.

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