REVERSE INSULIN RESISTANCE

FOR PATIENTS WITH INSULIN RESISTANCE AND HYPERINSULINEMIA

Evidence Based Medicine

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Written by the author of "Treating insulin resistance naturally" (available in German language)

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Basic guidelines to "reverse insulin resistance"

The concept of „conform nutrition", which is described in this booklet, was developed from patients who suffer from insulin resistance to help other patients coping with insulin resistance.

The concept was further refined by the help of physicians, nutritionists, and biologists.
The concept is based on scientific studies (evidence-based medicine) and personal experiences from patients coping with insulin resistance.

The concept presented here serves as a recommendation for patients with insulin resistance and hyperinsulinemia. As each patient presents a different medical history an adjustment of the concept might be required.

Using this concept cannot replace any kind of medical consultation (e.g., by a physician/nutritionist). A doctor must be consulted in case of any doubt!
We do not take any legal responsibility for the usage of this concept in any way.

Insulin resistance (IR)

Insulin, which is a peptide hormone, is produced by specialized cells of the pancreas, the beta cells. Insulin binds to the insulin receptor. This receptor is broadly expressed by different cell types of the human body. Insulin facilitates the uptake of glucose from the blood stream. Insulin resistance (IR) is a pathological condition under which certain tissues (e.g., liver and muscle) fail to respond adequately to insulin (this is also known as impaired glucose tolerance (IGT)). However, the pancreas can overproduce insulin to enforce the uptake of glucose into cells (a process called hyperinsulinemia). Therefore, an IR can be asymptomatic for many years [1]. If left untreated, IR and hyperinsulinemia can manifest in more severe diseases such as type 2 diabetes.

The exact causes that trigger IR are currently unknown. It is believed that many factors lead to the development of IR. A major component associated with IR is a genetic predisposition, leading to impaired insulin metabolism [2].

IR presents with a variety of symptoms and often varies in its severity between patients. This again makes IR tricky to diagnose. Following methods are commonly used to diagnose IR and determine its severity [3]:

***Direct Methods to diagnose IR*:**

- Hyperinsulinemic-euglycemic clamp technique (very precis but time intense, therefore not often used)
- Insulin tolerance test
- C-peptide suppression test / insulin suppression test

***Indirect Methods to diagnose IR*:**

- Bergman Minimal Model (to validate insulin and blood glucose measurements)
- Intravenous glucose tolerance test (IVGTT)
- Measurement of serum insulin
- Oral glucose tolerance test – paired with insulin testing
- The homeostatic model assessment (Homa Index)
- The quantitative insulin sensitivity check index (QUICKI)
- Matsuda Index

Of note: Postprandial hyperinsulinemia might present normal results in the above-mentioned tests although a patient has IR!

In addition, there is a variety of pathological conditions that are often associates with IR:

- Steatosis hepatis (fatty liver) [4]

- Dark discoloration of the skin (Acanthosis nigricans) [5]

- Hyperglycemia and Hypoglycemia

- Hypoglycemia-like symptoms also blood glucose is not significantly decrease (as for Postprandial hyperinsulinemia) symptoms often associate with stress (confusion, fatigue, weakness, and inability to think clearly).

- Obesity [6]

- Sleep apnea [7]

- Depression [8]

- Dementia/Alzheimer's disease [9]

- Type 2 Diabetes [6]

- Polycystic ovary syndrome (PCOS) and hyperandrogenemia [10]

- Hashimoto's thyroiditis [11]

- Cancer [12]

- Reproductive disorders [13]

- Metabolic syndrome [14]

Symptoms that might indicate IR:

- Feeling sleepy after food (predominantly after high-carb meals)

- Cravings (for sweet food/candy /binge eating)

- Problems in weight management (although following a diet)

- Fatigue

- Loosing focus

- Headache

- Migraine

- Joint pain

Of note: All symptoms can present in people with underweight, normal weight and overweight. Although falsely reported, IR is not strictly associated with overweight/obesity [15]. An IR should be treated to prevent further progression of the disease and to increase life expectancy. Since an undiagnosed and untreated IR often hampers day-to-day life the right diagnoses and treatment is important to improve the quality of a patient's life.

IR – Changing the daily habits to improve insulin sensitivity

To combat IR and hyperinsulinemia we suggest adapting to an IR conform lifestyle:

This new (conform) lifestyle includes:

1. IR conform nutrition
2. Physical activity
3. Stress management
4. Sleep routines
5. (if required) Medication.

An IR conform nutrition - Is my meal conform?

What is IR conform nutrition?

An IR conform nutrition (diet) is a diet that is adjusted to the requirements of a patient with IR (or Postprandial hyperinsulinemia). IR conform nutrition can be defined as nutrition with a low to moderate glycemic index (GI) and a low glycemic load (GL). Meals with a high GI result in a higher insulin spike compared to meals with a low(er) GI. Exactly these insulin spikes can lead to an increased physiological insulin level or even cause insulin resistance. The increase in insulin furthermore results in a lower sensitivity of cells towards this hormone, starting a vicious circle. The high production of insulin stresses the pancreas, damages beta cells and can lead to type 2 diabetes [16].

The glycemic index (GI) and the low glycemic load (GL)

The GI assigns numeric scores to food respectively to their ability to cause insulin spikes. Food that causes a (s)low increase in insulin will result in a (s)low to moderate increase of the blood sugar [16,17].

So what foods are good to avoid insulin spikes?

There are plenty tables available online that help to identify the GI of a product.

Based on what table one checks, products with a low GI have a GI <70[18].

But are all such products (with a GI<70) conform? No, the products can still be unfavorable and cause insulin spikes. More important than the GI is the GL. The GL is an assigned number that gives an estimation of how much the food will raise the blood glucose level. Accordingly, it can

be correlated with the insulin spike it will cause [19]. For IR patients it is important to consider the GI and the GL and presumable choose products with low values [20].

Still, for some foods, the classification can be complicated. Here an example:

Watermelon has a GI of 72, which is higher than the GI of toast.

The toast however has a higher carbohydrate density and therefore a higher GL.

The solution: Since the watermelon has rather few carbohydrates it has a GI of 4. Therefore, watermelon can be eaten if combined correctly.

The GL can be classified as follows:

Low GL: 0 - 10

Moderate GL: 11 – 19

High GL: 20 or more

When considering all foods consumed per day the classification is as follows [21]:

Low GL < 69

Moderate GL 70 – 119

High GL >120.

A great introduction to GI and GL can be found published by "The University of Sydney": www.glycemicindex.com.

Patients with IR and hyperinsulinemia should reduce processed food as much as possible. In addition, food that contains added sugar is not favorable for their condition. It might happen, that a product has a low GI but it has been highly processed. Here one should look for alternatives.

An IR conform diet should be based on unprocessed whole foods that are rich in vitamins and nutrients.

To be able to recognize hidden sugar in processed products one needs to know what ingredients sugars are. A guide can be found on our homepage (currently only available in German): www.insulinresistenz.club/download

Avoiding industrially granulated sugar can be an important factor when fighting IR. Sugar triggers our "reward system". It can be triggered similar as when consuming drugs [22]. In animal models it was seen that animals, once conditioned to eating sugar, presents withdrawal symptoms when sugar was removed from their nutrition [23].

Animal studies cannot be translated directly to human, but many people might know how difficult it is to cut down on sugar. Thus, it might be worth to reconsider which effects sugar has on our health but also on our brain. In addition to the before-mentioned aspects industrially granulated sugar plays an important role in developing an IR. The explanation is quite rational, by the consumption of cane sugar we cause insulin spikes. The combination of low levels of physical exercises paired with a bad nutrition (often high in processed sugar) can lead to reduced insulin sensitivity [24, 25].

A conform nutrition is thus a nutrition that stabilizes the blood sugar level and reduces insulin spikes.

Another important factor is the order of foods. It was shown that when protein rich foods and vegetables are eaten before the carbohydrate rich foods it had a positive effect on the blood sugar level and insulin spiking [26].

Another important aspect is the choice of the carbohydrate. The whole grain alternatives have several advantages compared to conventional products (e.g., pasta). One of them is the amount of fiber whole grain products have. Fiber slows down the insulin reaction as it is broken down rather slowly by our body. This also results in an effect that we do not get hungry soon again after a meal [27 - 29].

Resistant starch has a similar effect. Resistant starch is a carbohydrate that gets digested in the small intestine and ferments in the large intestine.

There are different types of resistant starches. Some are in whole grain products, some are in legumes and some develop by special treatment (cooking, frying, baking). Potatoes are an example of a vegetable that develops resistance starch after cooking and cooling down. The resistance starch in turn results in a lower insulin spike [30,31].

It is important to know that certain foods might get digested faster when they are cooked or take up water (compared to when eaten raw). Thus, this food might have a strong effect on the blood sugar and is therefore having a higher GI. A similar effect is seen when food is mashed or puffed, as e.g., commonly done for cereals [32].

As mentioned before, it is beneficial for patients with IR to **omit processed food**. Likewise, it is beneficial to reduce boiling time (e.g., by steaming). Carbohydrates should be combined with foods that contain fat- and foods that are rich in protein. Combining carbohydrates with fat and protein causes a lower insulin spike [16] [33,34].

An important aspect is further choosing **„good" fats**. Saturated fats or even trans fats (commonly found in e.g., Meat, Milk, processed food, Sweets) were seen to have a negative impact on the insulin resistance. Therefore, we should not consume them too often. „Good" fat sources are e.g., seeds or nuts [35,36].

Some advice for your day-to day cooking schedule:

- *Cook your meal „al dente" (so that it is still slightly firm).*
- *Do not cut too tiny pieces.*
- *Mashed food not the best when combating IR.*
- *Eat your carbohydrates in combination with fats and/or protein.*
- *Eat the vegetable before the carbohydrates to slow down the glycemic reaction.*
- *Take advantage of foods that form resistant starch: Let potatoes/whole-grain noodles or brown rice cool down after boiling.*
- *Avoid strongly processed food (such as puffed cereals or dried fruits)*
- *Try to compose your meal of 10-25% protein, 20-35% fat and 45-55% complex carbohydrates.*

IR nutrition- Low Carb (Yes/No)?

A low carb diet is a diet that drastically reduces the amount of carbohydrates per meal. There is currently no clear definition of „the low carb diet". Many types of low carb diets follow "rules" as in the following classification [37]:

- Very low carb diet
  → <10% (or 20-50 g/day)

- Low carb diet
  → <26% (or <130g/day)

- Moderate carb diet
  (26-44%)

- High carb diet
  → (more than 45%)

The lack of a clear definition and the different classifications (very low/moderate) make it difficult to generalize "low carb" diets - as people might refer to different principles.

The term „low carb" is often used, when a diet is (almost) free of carbohydrates. This nutrition is not favorable for people with IR. It is more important for people with IR to eat the "right carbohydrates" than omitting carbohydrates. Moreover, a diet with a moderate level of the "right" carbohydrates can increase insulin sensitivity [38, 39].

Consequently, an IR conform nutrition should include whole-grain products!

Since most foods contain carbohydrates by nature (including vegetables) one should try to reduce the amount of carbs coming from whole-grain products. We suggest that a major proportion of a meal should be vegetables/greens.

Theoretically, this would be a low-carb diet. However, for an IR conform diet it is best to not eat less than 130 g of carbohydrates per day. When checking with the classification list, our diet would fall into the category of a moderate carb diet. We try to omit the word low carb and normally refer to an IR conform diet. We feel that people who are not used to the vocabulary often get confused with the terminology and might mix up the concepts.

In summary, an IR conform diet includes carbohydrates:

- Always include suitable carbohydrates to your diet.
- It is best to use complex carbohydrates, whole-wheat flour, whole-grain products. Do not use refined wheat flour. Use flour from whole-grain cereals.
- Always combine carbohydrates with fat and protein.
- Do not eat less than 130g (carbohydrates) per day [40].

Legumes are a great option for IR conform nutrition

Soy and legumes are part of a plant family called the legumes. Legumes are rich in protein [41] and are therefore ideal for a balanced diet. Legumes are rich in fiber, are composed of complex carbohydrates and do not have cholesterol [42, 43]. Different studies showed that the implementation of legumes into the diet improves insulin sensitivity. A key factor seems to be their anti-oxidative factors. However, research shows that there are more mechanisms that might improve insulin sensitivity [44].

It was shown that some components in legumes a) increase the amount of glucose transport proteins on the cell wall [45 - 47], b) suppress the development and accumulation of adipose tissue [48, 49]. In addition, it was shown that legumes have a positive effect on cytokine secretion from adipose tissue [50, 46]. Finally, legumes are beneficial to build a healthy microbiota [51].
Another positive side effect is that soy and legumes have a variety of bio-active substances, so-called secondary plant compounds (such as carotenoid and chlorophyll) but also phytoestrogen (isoflavonoide) that were proven as beneficial to increase insulin sensitivity [48].
Soy, peas, lentils, and other legumes should therefore be eaten regularly as part of an IR conform diet. Important is to combine legumes with other food groups.

Vegetables are the foundation of an IR/hyperinsulinism conform diet

Vegetables are rich in vitamins, minerals, and fiber. Thus, vegetables are an essential part of a healthy diet. Various vegetables have a low GI / low GL and can therefore be eaten in huge amounts. It is recommended to eat around 250-300 g (raw weight/uncooked) of vegetables per meal since it fills up the stomach quite well. Patients with IR can even consume vegetables with a higher GI when they combine it IR conform.

Fruit

Like vegetables, fruits supply us with vitamins, minerals, and fiber. Once the IR treatment has begun there is no harm in including fruits with an appropriate GI/GL. When combined in an IR conform manner people with IR can eat all fruits. Amongst all fruits citrus fruits and berries cause the lowest glycemic reaction. Attention needs to be paid for bananas. Green bananas cause a lower insulin spike than yellow bananas. The right amount of fruits per portion is between 150 and 200g.

Nuts and Seeds

Nuts and seeds are calorie dense nutrients that contain great amounts of unsaturated fats, proteins, bioactive substances, and fiber (especially when the soft peel is not removed). Secondary plant compounds such as polyphenol are considered to act as antioxidants. Nuts improve the postprandial glycemic reaction, which leads to a higher IR sensitivity in muscle and adipose tissue. In addition, nuts are described to increase the production of hormones involved in satiety. One reason this could be explained by is that nuts require intensive chewing. Due to nuts being high caloric they were considered as "weight-gaining nutrients" for a long time. However, this was not proved scientifically [52]. We recommend implementing and combining nuts and seeds for an IR conform diet.

Beverages

A general recommendation is to drink at least 1.5 liter per day. Obviously, these amounts should not soda. Soda and other drinks with added sugar are likely to cause weight gain and are directly connected to IR [53]. Therefore, IR patients should not consume these drinks. It becomes more complicated with "light" beverages that include sugar alternatives (often called zero sugar). To date, correlation studies are missing to prove the effect of sugar alternatives on IR. Still, the mechanisms how these compounds work are not fully understood, yet. What has been shown is that the sweet taste triggers pathways that lead to increased appetite. This in turn might result in weight gain and cause IR [53, 54].

Another example are juices. Plenty of commercially available juices are highly processed and often even contain added sugar. Interestingly, some studies revealed that pure juice (with a fruit content of 100%) did not increase the risk of developing IR [55].

However, one should consider the bodies reaction to juice. In any case, a freshly pressed orange juice has more health benefits than Soda. But, in case your body reacts to the sugar in the orange juice it might be better to look for alternatives. In some IR patients the sweet taste acts as a trigger and causes cravings. This again has a direct effect on the IR. Each patient needs to identify he/her body and learn to understand how it reacts to certain foods/beverages. For an IR conform diet we recommend drinking water and unsweetened tea. (OBS! Be aware that tea blends often contain hidden sugar. So always check the packaging for hidden sugar and prepare tea from fresh mint leaves (e.g.) if in doubt). We recommend drinking between 1.5 and 2 liters per day.

This amount does not cover water/liquid that is included in a meal. For example: When milk is added to a coffee is counted as a meal as the milk contains quite some carbohydrates. As a recommendation, milk coffee would be best placed after a meal, to reduce any additional insulin spikes. Interestingly, caffeine free coffee can increase insulin sensitivity [56].

As an exception, one can also prepare a Smoothie. In comparison to commercially available juice the smoothie contains fiber. Please consider here again the GI/GL of the ingredients and do not blend it too long.

Meat and meat products

Regardless of ethical reasons, patients with an IR can eat meat as meat does not have a great impact on the glycemic reaction. Still, there are some aspects we should consider: processed meat, especially red meat has been shown to increase the risk of developing IR, diabetes, or metabolic diseases. Sausages do often contain added sugar, saturated fats, and high amount of salt, which can, if consumed in high amounts have also negative effects.
Salts (especially nitrites und nitrates) are often used to conserve sausages. These salts are considered to harm pancreatic cells and can thereby influence the insulin response.
It is further important how the meat is prepared. When fatty-protein rich meat is exposed to great heat (by grilling or deep-frying) advanced glycation end products can develop. Advanced glycation end products are toxins that can harm the body in different ways. They can lead to chronic inflammation, increased blood pressure, obstruction of the arteries and are also considered to cause IR [57].

Since IR and diabetes are complex diseases, the diet alone might not be the only problem that led to the onset of the disease. Often it is more helpful to reflect on the entire lifestyle/habits of the patient.
Therefore, the consumption of meat can only be a piece of the picture and needs to be considered for each patient individually. When consuming meat, we recommend selecting unprocessed meat. When consuming sausages, it is helpful to check the ingredients for hidden sugars.

How many meals shall I eat per day?

Patients that show high insulin spikes that present hyperinsulinemia (as measured by OGTT) are often recommended to eat 3 meals per day. The interval between each meal should be 4-5 hours to maintain a constant low insulin level. If this is not compatible with the lifestyle or one develops symptoms of hypoglycemia one can increase the number to 5 smaller IR conform meals. This is also a good guideline for people that show a low fasted insulin level but reveal high insulin spikes in an OGTT test. Again, it is helpful to listen to body signals, when the 3-meal strategy does not work well it might be better to include conform snacks to the diet. Fasting and especially intermittent fasting is a difficult topic. More and more people are interested in this diet as it is often used to reduce weight. It is proposed that fasting triggers stress signals that result

in an immune answer. This immune answer stimulates cell renewal leading to a positive metabolic state (low cholesterol, low blood pressure, reduction of body fat) [63]. Different animal studies revealed that a low caloric diet (achieved by intermittent fasting) results in an increased lifespan and an increased tolerance towards metabolic stress. Cohort studies, on the other side, have not been conclusive. Different studies have seen different outcomes which could be explainable by the different parameters (number of participants, duration of the study, no or insufficient control groups). In summary it can be said that some studies show that fasting leads to a reduction in body mass. However, there was no scientific evidence that intermittent fasting is more effective than other forms of calorie-restriction. Very interestingly, some studies showed that patients with IR tend to compensate their „fasted-calories " with high caloric intakes during their eating period. Intermittent fasting can, under certain circumstances (ideally under medical supervision), be beneficial for people without any metabolic disease and eating disorder [64].

> **Intermittent fasting is highly disadvantageous for people with diabetes, IR, any kind of eating disorder as well as infants, children, pregnant or breast-feeding women. In addition, patients that are taking certain kinds of medicines (including Metformin) should not fast.**

We recommend developing an eating routine that is based on 3 to 5 conform meals per day. In the ideal case the meals would be taken at similar times each day. Of course, this can be complicated for certain people so that adjustments might be needed. Help can be found in our insulin resistance Facebook groups.

Calorie restriction/Diets with IR

Patients suffering from IR and obesity should take care of their weight management. To do so, it is important to know the daily calorie intake and the daily calorie burn. There are several tools available online to calculate the average calorie burn. Advise can also be given from nutritionist who are educated to calculate these values. For a gradual fat loss, it is already sufficient to reduce the daily calorie intake by 500 kcal. Be aware, that the new value must not be lower than your basic consumption. Further help can be found in the Facebook group or on our homepage.

Additional parameters that increase insulin sensitivity:

The most important parameter is changing the diet/nutrition and changing the calorie intake. In addition, there are 3 further parameter that are crucial when fighting IR:

Physical activity

Physical activity results in a higher insulin sensitivity. Physical activity (including sports) increases the number of insulin receptors and increases the cellular response to insulin. It further increases the function and number of glucose transporters e.g., in muscle tissue. This in turn stabilizes blood sugar and insulin levels [65]. Physical activity leads to a higher calorie burn. Plenty of IR patients have reported about an improved insulin sensitivity and the loss of body fat after changing to an IR conform diet paired with physical activity.
Although people with obesity are predisposed to developing IR; IR can also be developed by people with a normal or even a low body weight [66].
It seems that people with a high percentage of visceral fat (organ fat), that is stored in the abdominal cavity, are more likely to develop IR. This can even be true in slim people that do not present typical signs of obesity. However, visceral fat is highly active and secretes chemokines and hormones, which can lead to the development of an IR [67] [68]. It could be shown that only 30 minutes of physical activity/ resistance training improve blood parameters related to insulin resistance and reduce the risk of developing type 2 diabetes [69] [70].

Stress management

Stress, especially chronical stress can lead to IR or favor the development of IR. One reason is the release of stress-related hormones (e.g., cortisol) that have a negative impact on sugar metabolism and the function of insulin receptors [71, 72]. Patients with IR should therefore decrease stress. Several studies on patients with pre-diabetes have shown that stress management improves blood pressure and mental state. These patients were less likely to develop depression and depression-related diseases [73, 74].

Sleep routine

Chronic sleep deprivation can alter cortisol levels and thereby alter blood sugar regulation and insulin sensitivity. Shortened duration of sleep was associated with a higher BMI and a higher risk to develop type 2 diabetes [75]. Accordingly, taking care of our sleeping behavior is very important for patients with IR.

The dietary supplement Inositol

Myo-Inositol and Inositol are supplements that are often used as additional support to treat IR. Myo-Inositol is a natural ingredient, that is commonly used to help to regulate periods, decrease androgen levels, IR and the management of polycystic ovary syndrome [58]. Inositol regulates hormones and periods. It has shown to be effective in women with PCOS [59] and men with desire for children [60]. Some other studies proved a positive effect for patients with anxiety [61]. In addition, insulin sensitivity was increased [62].

Metformin

Metformin is the first-line medication for the treatment of type 2 diabetes. It belongs to the chemical class of biguanides. In contrast to other medications – that are used to treat type 2 diabetes-metformin does not only decrease the blood-glucose level but also increases insulin sensitivity. Metformin further reduces the risk of developing cardiovascular diseases in patients with IR and type 2 diabetes. Another application is it used for is to treat PCOS. It is reported to improve ovulation, which in turn helps women to conceive. It is also reported to have anti-cancerous effects [62, 76].
A potentially very common side-effect is that it is easier to reduce body weight when taking metformin. This makes it a commonly prescribed drugs for patients with IR. Yet, metformin is not a weight-loss pill.
Metformin is a prescription medication that needs to be prescribed by a physician/Doctor.
We have seen that metformin does not work in all patients. This might be, as said before, that an IR can have different causes such as a genetic disposition. Some report about an improvement of their IR when metformin is taken, and an IR conform lifestyle is followed. Some others report about severe side effects and had to stop the medication.

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Plenty of patients use this concept, improved their health conditions even without taking metformin. For other patients' metformin was useful to treat their PCOS and helped them conceive and reduce the risk of miss carriage. Since metformin needs to be prescribed the possible usage of metformin can be discussed with a physician/doctor. One should also consider other alternatives (apart from metformin) and consult a fertility center when trying to conceive.

At the end

To date, plenty of patients have used the here described concept and successfully lost weight, reduced their symptoms, or even defended their IR. There are several ways to improve your IR. We feel that it does not have to be by following a very restrictive diet. Unfortunately, that is the way that is commonly recommended to patients with IR: "Please follow a No-Carb diet", "please follow intermittent fasting", "eat low-carb", "follow a ketogenic diet" have commonly been recommended. Unfortunately, these recommendations are helping for a while and are not easy to implement into a day-to-day routine. When stopping to follow these recommendations patients often feel that their IR returns and often even the lost weight returns. Nutritional concepts as therapy for insulin resistance should lead to a permanent change in lifestyle and must be integratable into everyday life. We believe that patients need to understand what IR and hyperinsulinemia are and what they can do to improve their health condition in their everyday life. Understanding and following these recommendations will help IR patients to combat their IR in the long-term and reduce the chance of developing secondary complications.
For questions and ideas please visit our homepage: www.insulinresistenz.club
Or write an email to insulinresistenz@gmail.com !

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