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The effects of aerobic and non-aerobic exercise regimes on muscular insulin resistance.

Moving towards a solution. **01-07-2021**

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Lifestyle-related diseases are increasing in tandem with the obesity epidemic. One of the biggest challenges facing public health is the increase in type 2 diabetes. Type 2 diabetes is an often preventable, lifestyle related metabolic disorder. The normal insulin-response to hyperglycemia is impaired, leading to a chronic hyperglycemia and in turn a hyperinsulinemia. The mechanistic cause for this insulin-resistance is often multifactorial; an aberrant signal transduction and inability to properly act on signalling pathways, abnormal lipid profiles and mitochondrial dysfunction are at play. A sedentary lifestyle contributes to the further development of insulin-resistance and metabolic disorders. Physical activity and especially a regimented exercise routine can improve insulin sensitivity; promoting muscle-remodeling for better nutrient delivery, improving receptor and post receptor signalling function as well as improving mitochondrial function.
Muscle tissue is heterogeneous, consisting of a mixture of slow-twitch (Type I) and fast-twitch (Type IIa and IIb) fibers. These fibers are responsible for different functions and respond differently to exercise. Aerobic exercise can be divided into moderate-intensity, high volume and high-intensity, low volume training. Both forms offer similar adaptive benefits. Resistance training offers similar, but distinct benefits in relation to insulin sensitivity. A combination of both aerobic and resistance training offers the greatest insulin-sensitizing effect. This review aims to investigate the nuance of insulin sensitivity and the importance of exercise.

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Introduction

In modern society, many non-communicable diseases have a far-reaching impact on public health. In 2016 the WHO estimated ~39% of adults to be overweight (BMI ≥ 25 kg/m^2) and ~13% of adults to be obese (BMI ≥ 30 kg/m^2) worldwide. This statistic is rapidly worsening, thus obesity is now considered to be an epidemic. The obesity epidemic emerges in all sections of health-care; it is associated with cardiovascular disease, cognitive dysfunction, non-alcoholic fatty liver disease, cancer, sleep apnea and type 2 diabetes (T2DM) (Mitchell et al., 2011).
One of the biggest challenges to the current healthcare system is dealing with the ever-growing number of diabetes patients that can often be traced back to obesity.

Diabetes mellitus is a multifaceted condition that leads to disease in various organs and disruption of normal physiological processes.
In stark contrast to the genetic cause of type 1 diabetes, T2DM is far more preventable, as T2DM is often caused and aggravated by lifestyle factors.

As stated earlier, obesity is often a major contributor to T2DM, however far more factors are at play in the development of insulin resistance and thus T2DM.

A sedentary lifestyle, meaning a constant lack of or far too little physical activity and a general reliance on sitting, is a major risk factor in the development of T2DM.
In relevant literature, sedentation is commonly defined in terms of time spent in sedentary behaviour. This description more adequately describes the actions of studied individuals than the term 'physical inactivity', which would mean that participants do not meet the daily recommended amount of exercise. This is a less accurate measurement, due its polar, yes-or-no quantification. Clear associations between the increased time spent in sedentary behaviour and T2DM are found, as greater sedentary time was linked to a 112% increase in relative risk for development of T2DM (Wilmot et al., 2012).

Not only is a sedentary lifestyle a risk factor, the inverse, regular physical activity, is a clear tool to prevent development or treat symptoms of T2DM.
As weight loss and especially caloric restriction is also a potent tool for management of ` (pre-)T2DM, it is important to not neglect this factor in researching benefits of physical activity (Franz, 2016). However, when adjusting for weight loss caused by the increase in physical activity, risk of T2DM development still decreases (Crisca et al., 2021).

The important role an individual's level of physical activity plays as a predictor for T2DM, can be explained by looking at the role of muscle tissue in glucose uptake.
Skeletal muscle is responsible for the vast majority of postprandial (directly following a meal) uptake of glucose. This glucose is taken up into the muscle via insulin-mediated transport and stored into the glucose-polymer glycogen. Thus, the muscles serve as one of the most important mechanisms to lower blood glucose levels in a hyperglycemic state (DeFronzo et al., 1981).
Its glucose storing capacities make muscle tissue a key topic of research in relation to T2DM. Therefore, next to the insulin-producing pancreatic β cells and the liver, muscle tissue is one of the most important targets for prevention and treatment of (pre-) T2DM.

This review aims to highlight the importance of undisrupted muscle glucose metabolism and the critical role of physical activity. In addition, important pathways for insulin signalling and the dysfunction of this particular process will be discussed.

Insulin signalling and muscle cell metabolism

Muscle glucose uptake can be either insulin-dependent or -independent.
Postprandial glucose uptake is mainly dependent on insulin signalling, as hyperglycemia is the primary insulin-releasing stimulus. After the meal has been digested in the gut, glucose is taken up into the bloodstream and distributed throughout the body. The glucose also reaches the Islets of Langerhans where the β cells are located. In response to the increased (insulin-independent) transport of glucose via the GLUT2-transporters, more glucose is taken up into these β cells. Due to the increased cytosolic glucose, the β cells will produce more ATP (Adenosine triphosphate) through glycolysis, shifting the ATP/ADP ratio. This process then acts as a stimulus for the depolarisation of the plasma membrane, eventually leading to secretion of granules already filled with insulin. Although the most potent stimulus, glucose uptake is not the only trigger for insulin release. Amino acids, free fatty-acids, other hormones and even bacterial components can also act insulinogenic (Baumgard et al., 2016).

After the secretion of insulin by the pancreas, insulin is distributed to peripheral tissues;
It binds to different organs like the liver, where it inhibits gluconeogenesis and other anabolic processes in addition to ensuring hepatic glucose uptake (Edgerton et al., 2017).
Insulin binding to muscle tissue also has a glucose lowering effect, however achieves this only directly. Through the insulin signal transduction (IST), glucose uptake from the bloodstream is significantly increased.
Insulin binds to the insulin receptor (IR), leading to the autophosphorylation of the cytosolic domain. This phosphorylation results in the activation of the insulin receptor kinase (IRK). Like most polypeptide hormones and growth factors, the IST is dependent on a tyrosine kinase signalling cascade. The IRK furthers the IST by phosphorylating a host of downstream molecules, namely the insulin receptor substrates (IRS-1 and IRS-2).
These substrate molecules are the base for the activation of various pathways via distinct signalling molecules such as PI3 kinase, producing the PI3K-AKT1 pathway, which is one of the main initiators of functions of insulin not relating to glucose transport. This pathway is in part responsible for the cell and body growth. The activated IRK-insulin complex is hereafter internalized and degraded by the endosomal insulinase (DiGugliemo et al., 1998).
To facilitate the transport of glucose into the muscle cell, specific glucose transporters are present that depend on IST. These GLUT4 (glucose transporter-4) proteins are tethered to TUG (tether containing a UBX domain for GLUT4) proteins, contained in GLUT-4 storage vesicles (GSV), only being translocated to the plasma membrane when IST occurs.
In response to the IST, a different signalling pathway, independent from the PI3K-AKT1 pathway, is initiated. This pathway seems to be heavily reliant on signalling through lipid rafts at the plasma membrane, with signalling through AKT2 and activation of the GTPase TC10α as main initiators. Through AKT2 signalling cascades, the PIST (protein interacting

specifically with TC10) protein cleaves TUG to thereby release GLUT4 from the tether at the Golgi-apparatus and translocate it to the plasma membrane (Cheng et al., 2007; Bogan et a., 2012).
The endoproteolytic cleavage of TUG occurs at its C-terminal (where it binds GLUT4) and at its N-terminal (where it is tethered to the Golgi-apparatus). Cleavage at the C- as well as the N-terminal is critical for the additional functions of TUG, which include the linking of GLUT4 to kinesin motors on the microtubules and a complex signalling pathway to initiate lipid oxidation and thermogenesis (Habtemichael et al., 2021). The mechanisms of TUG cleavage have only recently come to light, it was long unknown how insulin upregulated membranal GLUT4 expression. To date, the exact mechanisms for GLUT4 expression are not uncovered. Thus, to fully grasp the concepts and possible pathologies in insulin-related diseases, additional research is needed.

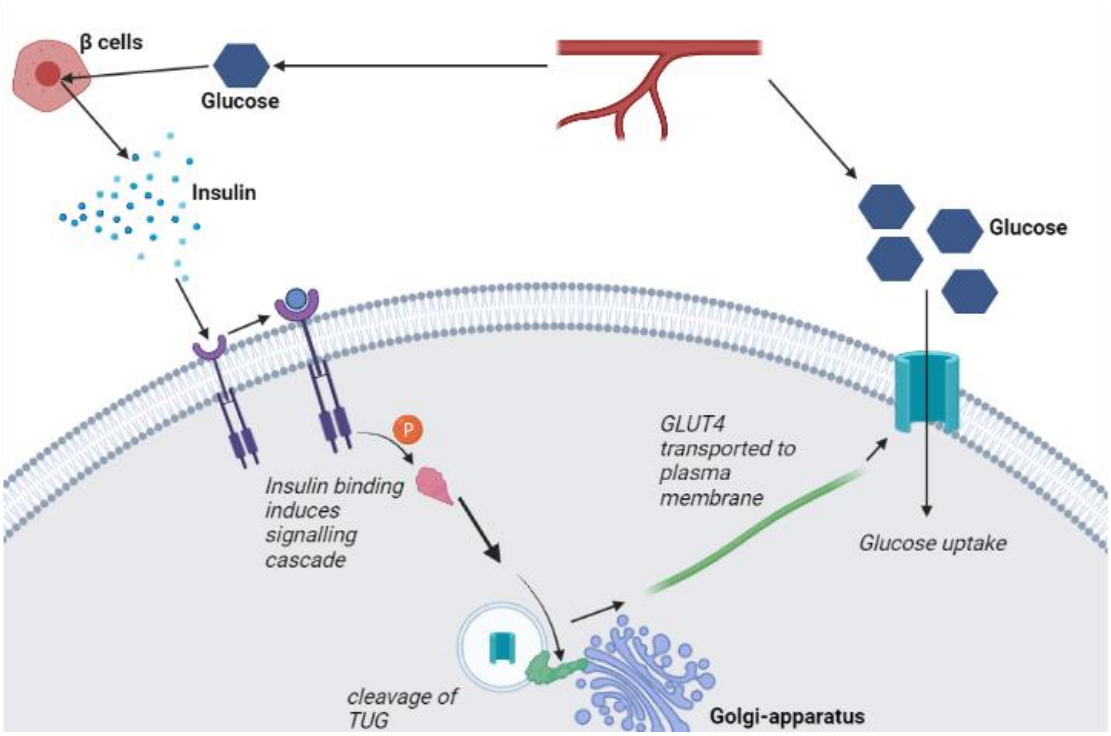

Figure 1: Insulin production and signalling in muscle cell. Glucose induces insulin production in β cells. Insulin binding induces the autophosphorylation of the cytosolic tyrosine-tail, which further transduces the signal. The signalling cascade induces cleavage of the TUG protein, which tethers GLUT4 to the Golgi-apparatus. GLUT4 is transported over microtubules to the plasma membrane and glucose is taken up.

Once glucose has been taken up into the muscle cell, it is either used in the glycolysis for energy or stored in glycogen for later use, depending on the energy needs of the cell. Particularly after a bout of exercise, the glucose will be used to replenish the muscle cell's glycogen stores or used for glycolysis in case of sufficient glycogen stores.
Not only does insulin increase glycolysis by increasing glucose uptake, but it also directly increases the rate of hexokinase and 6-phosphofructokinase to significantly upregulate glycolysis (dimitriadis et al., 2011). In line with the uptake of glucose, this process is stimulated by insulin.

Via IST, the principal enzyme responsible for glycogenesis, glycogen synthase (GS), is dephosphorylated and thereby activated. GS then uses the available glucose to add to the polymer.
A similar mechanism is seen in the storage of lipids in adipocytes, another energy storage system that is initiated by insulin (Lawrence et al., 1997).
In case of an energy deficit, such as during a bout of vigorous exercise, these glycogen stores are called upon to produce ATP via glycolysis.
Such production of ATP is fast, however not the most lucrative energy-producing system. Therefore, in longer bouts of exercise, the muscle cell will switch to the higher energy system of fatty-acid oxidation. These fatty acids are mainly retrieved from the triglycerides stored in the adipose tissue. The rate and characteristics of this fatty acid oxidation can determine the functionality of muscle metabolism (dimitriadis et al., 2011).
Apart from the glycolysis, all of these metabolic pathways are dependent on mitochondria. The cytosolic glycolysis is followed by extensive metabolism in the mitochondria and using the mitochondrial compartments to generate the bulk of the ATP. Namely the oxidative phosphorylation heavily depends on mitochondrial functioning, as the electron transport-chain relies on the polarity of its membranes. It is not difficult to imagine problems with this vital machinery lead to the dysfunction of other metabolic cell-processes.

Insulin resistance and muscle metabolism

Having looked at the normal insulin response, IST does not function as clear-cut in many individuals.
The many factors that interact with insulin production, binding and especially the signal transduction can make it far more complex.
With the onset of obesity and sedentary behaviour, more and more individuals experience insulin resistance.
Insulin resistance is the inability of an individual to respond adequately to hyperglycemia with insulin.
This can either be due to impaired insulin delivery to the receptor (e.g. presence of an insulin antagonist) or the lessened ability of insulin to elicit a proper IST via the IR.
The latter is often the cause of resistance. During the development of insulin resistance, the sensitivity to insulin is worsened over time. This increasing insensitivity to insulin and worsening dose-response relationship, further incentify the pancreas to produce more insulin. Eventually, the extent of the insulin insensitivity makes it impossible for the muscle cell to enable euglycemic conditions (Olefsky et al., 1981).

The mechanisms for the development of insulin resistance remain uncertain, however it is apparent that dyslipidemia is just as important as dysglycemia in causing T2DM.
In obese and insulin resistant individuals, circulating FFAs are increased. Serum FFA concentration is determined by the oxidation and storage rate. When these processes are not sufficient, the FFA concentration increases.

This aberrant lipid profile is a predictor of long-term hyperinsulinemia, which inhibits lipolysis and promotes de-novo lipogenesis in the liver. The inability to inhibit lipolysis, induces higher circulating free fatty-acids (FFA), due to the adipose tissue's inability to properly process these lipids. In addition, chronic hyperinsulinemia induces higher de-novo lipogenesis in the liver, as this insulin signalling is normally used to reduce gluconeogenesis and increase lipid stores. Therefore, this vicious pathological process of lipid metabolism dramatically upregulates circulating FFAs (Capurso et al., 2012).

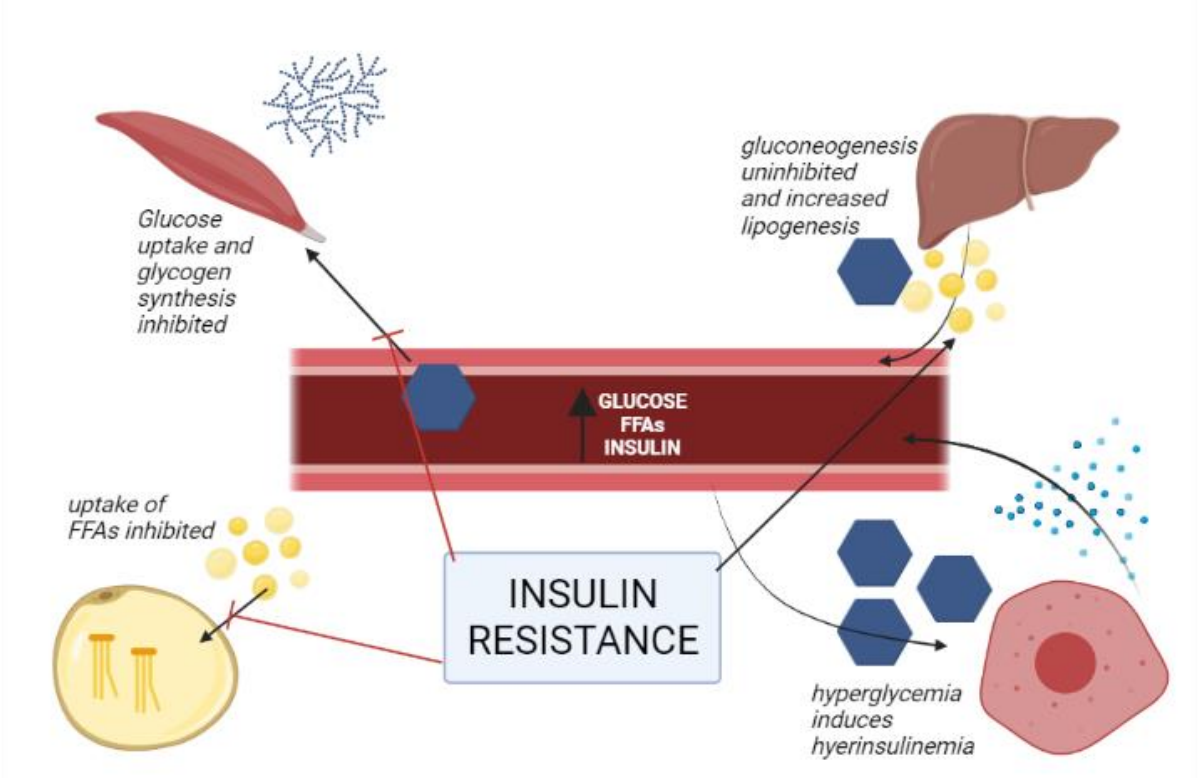

Figure 2: Schematic overview of insulin resistance. Insulin resistance induced by reduced IST, disallows the glucose and lipid homeostasis. Uptake of serum glucose and FFAs in muscle and adipocytes is inhibited. De-novo gluconeogenesis and lipogenesis in the liver is upregulated, in part by hyperinsulinemia. Glycogen formation in muscle tissue is lessened.
The high serum glucose and FFAs induce metabolic dysfunction and hyperinsulinemia.

Higher levels of circulating FFAs in turn leads to higher FFA content in the peripheral tissues, including muscle tissue.
This influx of FFAs alter the normal lipid content of the cell, especially at the level of the plasma membrane. This is of note, because the IST is highly dependent on the efficient functioning of lipid rafts and eulipidemia at the plasma membrane. In fact, the disjointed lipids can interact with the IR and IRS to dampen its signalling potential. A host of lipids have been studied to look at the effects their presence has on IST (Yu et al., 2002).
Ferrara et al. (2021) propose a mechanism in which the Land's cycle, responsible for the trans acetylation of phospholipids, is upregulated. This upregulation seems to be due to the overexpression of genes involved in the response to chronic overeating; LXRs and PPARs.

The higher rate of the Land's cycle could thereby disrupt the phosphorylation capacity of the IR and subsequent IRS and downstream signalling molecules.
Specifically, the LPCAT3 (lysophosphatidylcholine-acyltransferase 3) seems to be overactivated, which leads to an aberrant lysophospholipid profile. A fact supported by the fact that a LPCAT3 overexpression leads to increased glucose intolerance (Ferrare et al., 2021).
In addition to the disruption of normal membrane lipid profiles, evidence for mitochondrial involvement in insulin resistance is also abundant.
Roden (2002) proposes a model for mitochondrial dysfunction that is self-accelerating: either genetic or environmental (diet/exercise) factors impair mitochondrial function, leading to impaired fatty acid oxidation. This in turn leads to an impaired insulin-response, as explained above, which further aggravates mitochondrial dysfunction.
Furthermore, the effects of specific fatty acids differ between for example saturated and unsaturated fatty acids. Palmitic and stearic saturated fatty acids seem to have a particularly potent disruptive effect. Not only inhibiting the IST, but also impairing glucose oxidation. This impaired glucose oxidation in turn leads to increase in lactate and flux through glycolysis and fermentation pathways to compensate for the oxidative phosphorylation (Hirabara et al., 2010).

Muscle remodelling after exercise

Having looked at the (impaired) insulin response and cell metabolism, we can now see what impact exercise has on the insulin resistant and healthy muscle cells.
To perform its glucose-storing functions the muscle cell needs to be able to effectively take up glucose, store it as glycogen and metabolise glucose and lipids in the mitochondria, as mentioned above.
As it turns out, post-physical activity remodelling acts on all of these vital muscle functions. The stress induced by a bout of exercise conveys a need for better metabolic functioning in the muscle cells to be able to handle the next stressor better.

Firstly, the delivery of glucose and insulin to the periphery is highly reliant on function of the extracellular matrix (ECM). The composition of the ECM is highly important for the intercellular- and cell-to-ECM signalling, making it an important factor in insulin resistance. Individuals with hypertension, dyslipidemia, obesity and, most importantly, insulin resistance often suffer from a thickened ECM. This thickening of the ECM is characterized by higher expression of collagen Type I and III fibers and a thickened capillary basal membrane. Breakdown and remodelling of the ECM is achieved after a bout of exercise through heightened expression of MMP-9 and decrease in TGF-β1-SMAD2/3 expression. These genes are responsible for breakdown of ECM and ECM growth respectively.
This process allows for better blood delivery and an overall higher insulin delivery to the IR (Dantas et al., 2020).

Secondly, the benefits of exercise are measurable at the level of the IR as well. As the muscle is activated and contracts during exercise, the muscle requires energy.

At first, the muscle will use the limited free ATP in the cytosol, quickly thereafter switching to the ATP-storage system of creatine-6-phosphate, finally calling upon stored glucose in the glycogen molecules. When glycogen stores are also depleted, post-exercise, the muscle cell is in need of a new glycogen store. This is achieved not only by insulin-signalling, but also due to the decreased ATP/ADP ratio within the cell. This disturbed ratio is a signal for the cell to take up glucose, without the need for IST. In addition, the insulin-stimulated glucose uptake is also increased. This seems to be caused by an increased localisation of IR associated signalling molecules such as IRS-1, PI3-K and AKT. The increased localisation offers the IR more ability to transduce the stimulus from the binding of insulin, which is often impaired in the insulin resistant cell (Wojtaszweski et al., 1999).

Thirdly, the muscle cell's reduced capability to store glucose in glycogen molecules is often one of the hallmarks of insulin resistance.
A bout of physical activity provides the muscle cell with a need for glycogen synthesis, this signals for the processes involved in recruitment of glucose and synthesis of glycogen to initiate. However, insulin resistance is a disrupter of normal glucose metabolism and recruitment. Many research groups have found the glycogen production of an insulin resistant individual to still be less than a healthy individual after exercise.
However, the response to exercise seems to have a drastic sensitising effect on the muscle. Hexokinase, the enzyme responsible for trapping glucose in the cell through phosphorylation, activity is increased after exercise. This important effect of muscle contraction is measurable as the normalization of glucose-6-phosphate concentrations.
In addition, GLUT4 transporter numbers increase even after 1 bout of exercise, accelerating glucose uptake. The combination of these processes are of high significance, as a structured workout regime has been reported to increase whole-body insulin sensitivity by 40% (Perseghin et al., 1996).

Finally, impaired mitochondrial function is linked to impaired fatty-acid oxidation and dysfunctional insulin signalling. Mitochondria are extensively interlinked with insulin sensitivity, as the mitochondria are responsible for further utilisation of glycolytic products that are derived from glucose as well as fatty-acids. After the cytosolic glycolysis has yielded some ATP, the mitochondria uses pyruvate (from the glycolysis) and Acetyl-CoA (in part from fatty-acid oxidation) to fuel the TCA (tricarboxylic acid) cycle and the oxidative phosphorylation to generate the bulk of the ATP. However, this process does not function adequately in insulin resistant individuals. A higher dependency on the glycolytic pathway and less flux through the aerobic usage of glycolytic products, further decreases mitochondrial function. Exercise, fortunately, also heavily affects mitochondria.
Mitochondrial numbers are increased after a bout of exercise and after following a long-term exercise program. This is due to the increased organelle biogenesis that is triggered by the increased ROS-stress released during intense exercise. In addition to increased numbers, the individual mitochondrial functioning is also increased. The functioning can be seen in the increased mitochondrial respiration rate, which is normally impaired in insulin resistant individuals. A lower rate of mitophagy, the autophagy of mitochondria, is also observed. This is another strong suggestion that fewer mitochondria are dysfunctioning and are therefore in need for mitophagy (Memme et al., 2021; Kim et al., 2019).

Aerobic training versus non-aerobic training

After looking at the vast amount of insulin sensitising benefits of physical activity, it is important to distinguish different forms of training.
Two main forms of exercise (and their subdivisions) are to be recognized; aerobic or endurance training and non-aerobic or resistance training.
When examining these forms of exercise training, it is important to keep in mind that skeletal muscle tissue is not homogeneous. In fact, an array of different muscle fibers work together to enable the body to perform different modalities of mobility.
For example, the process of running a marathon is vastly different from sprinting a 100 meter dash or lifting a heavy weight. These differences are present in the molecular characteristics of muscle fibers.
Three main groups of muscle fiber have been proposed: Type I (slow-twitch) and Type IIa and Type IIb (fast-twitch) muscle fibers. A further classification is often made in Type II fibers, as many small differences are to be found within the type IIa and IIb fibers.
However, for the contents of this review, this is not relevant to our discussion of insulin resistance.
Type II muscle fibers use ATP at a much higher rate than Type I fibers, this enables them to contract significantly faster. However, slow-twitch fibers utilize oxygen, whereas fast-twitch fibers (mostly) do not.
Therefore, fast-twitch can contract at a higher rate and generate more force in a short period of time, but also fatigue much faster.
In this distinction, it is important to mention that Type IIa fibers do use some oxygen for their metabolism, however to a lesser extent than Type I fibers.
Type II fibers have a far higher ATPase activity, enabling the rapid hydrolysis of ATP for energy. Furthermore, the muscle uses the glycolytic pathway almost exclusively, due to its rapid ATP producing capability. However, because the oxidative phosphorylation is not used, high amounts of lactate are produced, leading to increased fatigue.
In contrast, the Type I fibers are reliant on the complete respiration of glucose and have a higher number of mitochondria, making it far less prone to fatigue. These fiber types are not solely expressed in a particular muscle, a heterogeneity exists, the relative abundance of each type determines the characteristics of the muscle (Bottinelli et al., 2000).

This heterogeneity of muscle fiber types is also seen in their response to exercise. As Pataki et al. (2019) showed, typically type I fibers are less insulin-resistant than type II glycolytic fibers, but also respond less dramatically to the insulin-sensitising effect of exercise. A possible explanation for this could be the significantly lower reliance on glycolysis and therefore less need for glucose uptake immediately following exercise. Their use of oxidative phosphorylation enables them to respond to the need for energy with a relatively lower needed glucose influx. In addition, Pataky et al. hypothesize that the insulin-sensitising effects of exercise might not be measurable immediately following exercise. Their measurements are only at 3 hours after the bout of exercise, which might be too short of a timeframe for the slow-metabolising type I fibers.

After having looked at the different muscle fiber types, the type of exercise also has a significant effect on the benefits in regards to T2DM. Namely, the differences between endurance and resistance training.

Firstly, within non-resistance training, a distinction can be made between aerobic, moderate-intensity (MI) endurance training (e.g. a bike ride at a moderate pace) and a more anaerobic, high-intensity (HI), interval-based style of training (e.g. HIIT; high intensity-interval training).

In the literature, this distinction is often further annotated in respect to the volume of training; where MI is performed with high volume and HI is performed with a much smaller volume. Although the two forms of exercise seem very different, where one relies heavily on type I fibers and the other far more on the use of glycolytic, fast-twitch Type II fibers, the results in terms of fitness seem similar. Burgomaster et al. (2008) reported an almost identical muscle remodelling response and mitochondrial markers for glucose and lipid metabolism.

As discussed in the previous chapter, these processes are of great influence for the development of a better insulin sensitivity. A major indicator that these two forms of exercise elicit similar metabolic benefits is found in the concentrations of muscle PGC-1α (peroxisome proliferator activated receptor gamma coactivator 1 α).

PGC-1α is one of the key regulatory proteins in the activation of mitochondrial biogenesis, acting on many genes responsible for translation of mitochondrial structural proteins. Another trial looking at more in depth markers for insulin resistance by Babraj et al. (2009) found similar results. Their trial used a remarkable low-volume of only ~250 kcal of work exerted weekly in HIIT sessions. Their results showed glycemic control improvements similar to MI, high-volume work when looking at serum NEFA (non-esterified fatty acids), muscle GLUT4 abundance and insulin-glucose responses. Their hypothesis for the high adaptations seen from such a small volume of physical activity, is the fact that, due to the high metabolic stress induced by this type of exercise, the muscle cell is forced to use much more of its glycogen stores than in MI. A potential downside to HI training is the high amount of strain it has on the body. It could be hard to perform, potentially dangerous and evidently impractical for severely obese patients or cardiac patients. Although evidence shows the latter group has a insignificant risk for suffering a (lethal) cardiac event as a result of HI training (Wewege et al., 2018).

Therefore, it is safe to conclude that, in terms of improvements to insulin resistance, both MI- and HI exercise seem to be an adequate form of non-resistance training.

Both styles of exercise come with unique benefits and downsides; as MI is less taxing and stressing to the body, it should be easier to perform. However, to be effective, MI needs to be performed at a high-volume, whereas HI requires less volume and therefore less time investment.

Next, resistance training offers an additional important exercise protocol for insulin resistance. Resistance training is an anaerobic style of training, where the acute contraction of fibers and rapid force production are trained. Due to its high demand for fast energy, this type of exercise utilizes glucose and glycogen to a much higher extent than MI endurance training and even HI interval training. In addition, resistance training induces hypertrophy, the process of muscle fiber growth. Growth of muscle leads to a higher amount of metabolically

active tissue and therefore a higher need for energy. Therefore, resistance training offers an inherent insulin-sensitizing effect. This effect is especially potent in older individuals, a patient group often suffering from reduced skeletal muscle mass or even severe sarcopenia (Dhillon et al., 2017). This would lead to believe that this style of training offers an additional, unique insulin sensitizing effect. Indeed literature points towards the benefits of resistance training: a regimented resistance training protocol offers a reducing adiposity (which on its own improves insulin resistance) and an improved glucose response (Guedes et al., 2019).

Finally, one would speculate on what training program would offer the highest amount of benefits. Is it advisable to focus more on the adaptations through aerobic-based training, do the benefits from resistance training supersede those or is a combination of them the most effective?

The DARE (Diabetes aerobic and resistance exercise) clinical trial by Sigal et al. (2007) compared the results obtained from aerobic exercise alone, resistance training alone and a combination of both exercise types. They used a sedentary control group to compare all of the aforementioned exercise groups. Measured parameters were: hemoglobin A1C (a representative parameter for the 3 month blood glucose levels), blood lipid levels, blood pressure and body composition (as the adiposity is a predictor of T2DM).

As it turns out, individuals with poor levels of hemoglobin A1C benefit from both forms of exercise; use of either aerobic or resistance training improves glycemic control. However, individuals with healthy baseline hemoglobin A1C levels did not benefit significantly from following either forms of exercise alone compared to the sedentary control group. Interestingly, when the combination of both exercise forms was followed, these healthy, relatively insulin sensitive individuals improved on their hemoglobin A1C levels. Thus, these results would suggest that the combination of both exercise forms, offers a stronger stimulus for insulin-sensitivity. This theory is further supported by the fact that insulin resistant individuals improved their glycemic control to a higher extent when taking part in both forms of exercise rather than just one of the two. The inclination that the two forms of exercise each offer a distinct insulin-sensitizing effect, is supported by these findings. Of note is the study design: the participants did not spend equal time exercising in all groups. In the groups that performed both forms of exercise, additional exercise time was performed. This could suggest the greater benefits of combining exercise forms to be solely contributable to the larger amount of exercise. However, as the authors state, both exercise forms do contribute to different systems supporting better insulin sensitivity.

These finding are consistent with additional literature suggesting the additive effect of using both exercise forms (Davis et al., 2011; Marini et., 2018). Inevitably though, additional trials with equal time spend exercising in all participant groups should be conducted.

Discussion

This review offers a comprehensive overview of the insulin response to hyperglycemia. This response is often impaired in modern society, as the obesity rates rise which are strongly linked to the development of T2DM. Insulin sensitivity is decreased as a result of disturbances in glucose and lipid metabolism. The muscle tissue is an important regulator of glucose levels, due to its high glycogen storing ability.

To tackle this problem, this review tries to highlight the grave importance of an active lifestyle; with a sedentary contributing to the development of T2DM and physical activity being a potent treatment option. Aerobic exercise, whether MI-high volume or HI-low volume, and resistance training are both predictors of improved metabolic health and glycemic control. Whether an individual should perform aerobic exercise at a MI or at a HI is not solely a case of clinical trial outcomes. In the long haul, improvements to metabolic health and health in general are determined by consistency. The continuous performance of the exercise regime prescribed is the most important factor in the eventual results. Ultimately, HI is a far more strenuous form of exercise, which could be a negative influence on its performability. The additive effects of resistance training are to be explained by its alternative mode of post-exercise muscle remodelling. The combination of both forms of exercise is the most potent treatment option for improving insulin-sensitivity.

In fact, a treatment with a strict exercise regime is under prescribed. Often, the treatment of early insulin-resistance and other metabolic disorders is sought in medication.
Metformin is a drug that has long been an effective treatment of T2DM.
Its use is associated with a dramatic increase in insulin sensitivity and little side-effects. However, the exact mechanism by which this medication improves insulin sensitivity is not known. The eventual results of almost all medication use is associated with mild to extreme side-effects that reduce quality of life.
Interestingly, intervention in lifestyle offered greater benefits than metformin use.
Knowler et al. (2002) reported 58% diabetes incidence reduction, while metformin reduced incidence with 31%.
This difference should however be placed into a realistic context; the case against lifestyle intervention to treat diabetes is twofold.

Firstly, the results from all of the exercise trials in this review are based on a strict exercise regime. In this regime, the participants have a high degree of external motivation: often they are guided professionally throughout the whole process and might even get a financial reward for completing the study participation. Real life, unfortunately, is far more uncertain. Many individuals are unable, or at the least are not willing, to make time to follow an extensive exercise regime. The cumulative time investment of work, family, errands and social life often supersede the capability or willingness to perform the needed exercise.

In addition to time constraint, some individuals, especially heavily insulin-resistant individuals, do not have the same increase-in-fitness as others.
For example, hyperglycemic conditions seem to prevent muscle remodelling and aerobic adaptations to exercise in a portion of insulin-resistant individuals (MacDonals et al., 2020). Thus, in some cases it might be necessary to treat severe insulin-resistance with metformin or other T2DM therapies. However, exercise should never be underestimated, as its benefits

are far-stretching. Putative effects are not reserved diabetics, as exercise is vital for slowing or reversing progression of other diseases. Of note is the extensive benefits of exercise for cardiac patients, as most exercise forms train mainly the cardiac muscle.
Considering that a large proportion of T2DM patients are overweight or obese, many of them will also be at a large risk for cardiovascular disease or are already a cardiovascular patient. Exercise is therefore not only an important consideration in management of T2DM, but in the management of overall health.

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