Bachelor's project

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Resistance Training in Type 2 Diabetes Mellitus Treatment and Prevention: An Overview of Underlying Mechanisms

Bachelor's project in Human Movement Science
Supervisor: Tonje Pedersen Ludvigsen
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ABSTRACT

English: Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin signaling and insulin resistance, thus an impaired glucose uptake leading to hyperglycemia. Obesity and physical inactivity, via inflammation and insulin dysfunction, are major risk factors potentially causing T2DM. Resistance training (RT) is recognized as effective in combatting this disease. The purpose of this literature study is to review the molecular and cellular mechanisms underlying the effect of RT as a therapeutic and preventive intervention for T2DM pathophysiology. A literature search was conducted, and results from 8 randomized controlled studies investigating RT-related mechanisms in T2DM treatment and prevention were included. Based on the included studies, RT seems to mitigate T2DM complications by positive alterations in insulin signaling, glucose uptake, inflammation, lipid profile, and oxidative metabolism. Several signaling proteins, glucose transporters, and inflammatory markers emerge as important components affected by RT contributing mechanistically to T2DM improvements. RT may also affect T2DM beneficially by increased expression of genes related to oxidative metabolism.

Norsk: Type 2 diabetes mellitus (T2DM) er karakterisert av nedsatt insulinsignalisering og insulinresistens, og dermed svekket glukoseopptak som fører til hyperglykemi. Fedme og fysisk inaktivitet via inflammasjon og insulindysfunksjon er store risikofaktorer som potensielt forårsaker T2DM. Motstandstrening (MT) er anerkjent som effektiv for å bekjempe denne sykdommen. Hensikten med denne litteraturstudien er å kartlegge de molekylære og cellulære mekanismene som ligger bak effekten av MT som en terapeutisk og forebyggende intervensjon for T2DM patofysiologi. Et litteratursøk ble utført og resultater fra 8 randomiserte kontrollstudier som undersøkte MT-relaterte mekanismer i T2DM-behandling og forebygging ble inkludert. Basert på de inkluderte studiene ser det ut til at MT reduserer T2DM-komplikasjoner ved positive endringer i insulinsignalisering, glukoseopptak, inflammasjon, lipidprofil og oksidativ metabolisme. Flere signalproteiner, glukosetransportører og inflammatoriske markører dukker opp som viktige komponenter som er påvirket av MT og som mekanisk bidrar til T2DM-forbedringer. MT tyder også til å påvirke T2DM gunstig ved økt ekspresjon av gener relatert til oksidativ metabolisme.

1.0 INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease in which the body is unable to utilize insulin properly (1). Insulin is a hormone secreted from the β-cell in the pancreas which regulates blood glucose levels (1,2). T2DM is characterized by insulin resistance (IR), where cells exhibit a lower sensitivity towards insulin (2–4), and in some cases β-cell dysfunction with insufficient insulin secretion, both of which can lead to a harmful elevation in blood glucose levels (hyperglycemia)(2–4). Glucose uptake transpires after insulin-binding induces phosphorylation of insulin receptor substrates (IRS's)(5). IRS's, mainly IRS-1 in skeletal muscle, activates phosphatidylinositol 3-kinases (PI3K), a participant in subsequent activation of other signaling molecules like protein kinase B (Akt/PKB) involved in Glucose transporter type 4 (GLUT4) vesicle translocation to the cell membrane (5). The GLUT4 protein facilitates transport of glucose in to the cell (5). Through these mechanisms, insulin facilitates the transport of glucose from the blood into the body's cells during energy-usage and -storage (1).

The pathophysiology of T2DM is characterized by several contributing factors. Common among them is their potential to disrupt the mechanisms outlined above, mainly at post receptor sites (2), inadvertently leading to IR and hyperglycemia (2,6,7). Physical inactivity, excess body weight, and genetic predispositions are strongly associated with these disturbances, and are the main factors increasing the risk of developing T2DM (1–4). Obesity and physical inactivity may lead to chronic inflammation, another hallmark of metabolic diseases (6). Adipocytes under metabolic stress, produce several inflammatory cytokines (6). Elevations in high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) increase in diabetics (8). Increased TNF-α is possibly involved in impaired Akt/PKB function (9), as well as suppressed insulin receptor and IRS-1 activity (4,10). In this fashion, excess body fat in conjugation with inflammation impairs insulin signaling and reduces glucose uptake (4,9,10). In addition, fatty acid metabolism in skeletal muscle is dysregulated in obesity and T2DM, which may result in the accumulation of lipids within the cells of the muscles (3). This may result in interference with insulin signaling, contributing to skeletal muscle IR (3). Lipid irregularities may also contribute to β-cell dysfunction (2).

Impairments in the mechanisms facilitating glucose uptake in skeletal muscles are of great importance in T2DM (2,5–7). This is because skeletal muscles are a major site for glucose uptake in the body, responsible for 80-90% of insulin-stimulated glucose disposal (2,11). These impairments culminate in the reduction of skeletal muscle capabilities of glucose uptake and transport (2), eliminating an important glucose-clearance organ, subsequently leading to hyperglycemia (11). Skeletal muscle IR is therefore a hallmark of T2DM (2,7). Exercise training (ET) is thusly an important intervention in combatting IR and T2DM by contributing to improved glucose homeostasis (2,5,7). ET is shown to mitigate several of the critical components of T2DM pathophysiology, including obesity and inflammation, as well as improving glucose transport and uptake, insulin signaling and insulin sensitivity (2,5–7,12). It is also assumed that the noted reduction in chronic inflammation is independent of the obesity-reducing effects of ET (6). In this regard, both the American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) endorse ET as an effective intervention in the treatment and prevention of T2DM (12).

One of the most common and effective forms of ET in improving T2DM and its associated complications is resistance training (RT) (12–14). In addition to combating T2DM pathophysiology, RT is regarded as a good exercise alternative to individuals that find other forms of ET too physically challenging (12,14). However, there is still limited insight into how RT mechanistically mitigates T2DM complications (3,4). For this reason, this literature study aims to review the molecular and cellular mechanisms underlying the effect of RT as a therapeutic and preventive intervention for T2DM pathophysiology.

2.0 METHODS

The literature search conducted in this study was carried out using the databases ORIA and PUBMED. Using the keywords “T2DM or prediabetes”, “RT or strength training”, “molecular or cellular mechanisms”, and “prevention or treatment/therapy”, initially resulted in 275 matches in ORIA, and 62 in PUBMED. Articles included had to be published in English, peer-reviewed, conducted on humans or animals, and keywords had to be presented in title, abstract or keywords. Articles were excluded if they solely studied AT or ET, a combination of AT and RT, or neglecting the underlying molecular or cellular mechanisms and focusing on the objective results RT has on T2DM. 27 eligible reference lists of recently published systematic reviews and/or meta-analysis were manually searched to identify any articles meeting the criteria that were not found through primary search. The filtration process resulted in 8 eligible articles (5 articles (8,15–18) from search, and 3 articles (14,19,20) retrieved from reference lists (3,12,21)) where two are based on rodent studies.

3.0 RESULTS

3.1 – CATEGORIZATION OF RESULTS

Based on the 8 articles obtained from the search, it appears that the role RT plays in positively effecting T2DM pathophysiology fits three descriptive categories of mechanisms, all contributing to glucose uptake and insulin function. These are apparent as mechanisms related to insulin signaling and glucose uptake molecules, inflammatory cytokines, as well as mechanisms affecting lipid levels and fat oxidation. Consequently, mechanisms of interest are henceforth presented and discussed categorically accordingly: RT and alterations in insulin signaling and glucose uptake related molecules, RT and alterations in inflammation, and RT and alterations in lipids and oxidative metabolism of adipose tissue.

3.2 – STUDY DESCRIPTION AND RESULTS

Due to the aim of this study, results from groups who performed other forms of ET than solely RT were excluded (table 2). Hence, from the 8 included articles (8,14–20) a total of 89 humans and 56 rats are distributed between either an RT group or a control group (table 1). Additionally, although some groups may be regarded as controls in their affiliated study, all groups performing RT are regarded as an intervention group (IG) and placed in the intervention column (table 2). 7 of the studies (8,14,16–20) performed chronic training programs between 4-16 weeks, while Bittel et al. (15) performed one single bout of RT (table 1). To be noted, Wojtaszewski et al. (19) is part of the larger Holten et al. (14) study, and therefore have comparative protocols (table 1). However, the studies have different aspects of interest regarding insulin signaling. Furthermore, 3 studies (14,19,20) only compared differences between baseline and after intervention, not pointing to comparisons with a control group. Thusly, if the corresponding control group is not specified in the control column (table 2), the right column presents the degree of significant difference in alteration from baseline.

The results presented in table 2 show that several mechanisms related to insulin function and glucose uptake were affected by RT. Regarding the insulin signaling cascade, alterations in key molecules, namely IRS-1, PI3K, Akt/PKB, and AMPK, were observed. In addition, alterations in glucose transporters were observed in several studies, most notably GLUT4. Inflammatory markers

like TNF-α, Interleukin 6 (IL-6), and hs-CRP also exhibited RT-induced alterations. In a similar fashion, RT affected lipid levels and fat oxidation.

***Table 1** – Study characteristics and specific aspects of interest affected by the intervention.*

Ref	*n*	Age	Subject description	Training protocol	Aspects of interest
Bittel et al., 2020*(15)*	10	50±9 years	Overweight/obese (BMI: 33 ± 3 kg/m^2) Sed. M with prediabetes.	IG: Whole-body RT. 3 x 10-12 reps at 80% of 1-RM. Con: resting condition. Acute (1 bout) 60 min.	Lipids, abdominal adipose tissue & muscle gene expression.
Talebi-Garakani et al., 2013*(8)*	24	~12 weeks	Non-T2DM M rats. Con, DC & DT-IG (all *n*=8).	DT-IG: whole-body RT. 1 x 10 reps with 30% of BM and progressed to 50%. Con & DC: usual care. Chronic (4 wk) 60-90 s 3x/wk.	Inflammation.
Abd El-Kader, 2011*(20)*	20	34-56 years	Overweight/obese (BMI 31-35 kg/m^2) with T2DM of both sexes (both n=10).	IG: whole-body RT. 3 x 8-12 reps at 60–80% of 1-RM. Chronic (12 wk) 40 min.	Inflammation.
Jorge et al., 2011*(16)*	24	53±9 years	Overweight/Obese F (*n*=15) & M (*n*=9) with T2DM. IG & con. (both *n*=12).	IG: whole-body RT. Con: light stretching. Chronic (12 wk) 60 min 3x/wk.	Insulin signaling molecules, lipids & inflammation.
Castaneda et al., 2006*(18)*	18	65±8 years	T2DM of both sexes. IG (*n*=13) & con (*n*=5).	IG: whole-body RT. 60-65% and progressed to 75-80% of 1-RM. Con: usual care. Chronic (16 wk) 45 min 3x/wk.	Glucose transport proteins.
Wojtaszewski et al., 2005*(19)*	17	62±2 years	T2DM (*n*=10) & healthy con-IG (*n*=7) with no family history of T2DM.	IG & con-IG: lower body RT. 3 x 10 reps at 50% and progressed to 8-12 reps at 70-80% of 1-RM. Chronic (6 wk) 30 min 3x/wk.	Insulin signaling molecules.
Holten et al., 2004*(14)*	17	62±2 years	T2DM (*n*=10) & healthy con-IG (*n*=7) with no family history of T2DM.	IG & con-IG: lower body RT. 3 x 10 reps at 50% and progressed to 8-12 reps at 70-80% of 1-RM. Chronic (6 wk) 30 min 3x/wk.	Glucose transport proteins & insulin signaling molecules.
Krisan et al., 2004*(17)*	32	~6 weeks	Non-T2DM M rats. Con, Con-IG, HF-Con & HF-IG (all *n*=8).	HF-IG & Con-IG: lower body RT. 3 x 10 reps at 75% of 1-RM. Con & HF-Con: sed. usual care. Chronic (12 wk) 12 min 3x/wk.	Glucose transport proteins & insulin signaling molecules.

***BMI:**body mass index, **T2DM:**type 2 diabetes mellitus, **M:**male, **F:**female, **IG**:intervention group, **RT:**resistance training, **reps:**repetitions, **min:**minutes, **Con:**control, **n:**number, **~:** approximately, **1-RM:**one-repetition maximum, **Sed:**Sedentary, **HF:**High-fat, **BM:**body mass, **DC:**diabetic control, **DT**:diabetic traiuned, **s:**seconds.*

Table 2 *– RT induced alterations in insulin signaling and glucose uptake related molecules, inflammatory cytokines, lipid levels and fat oxidation. Alterations are presented as a comparison to baseline values (arrows), and with corresponding control group.*

Effects on insulin signaling and glucose uptake related molecules				
Ref	**Signaling molecules**	**Intervention**	**Control**	**Intervention vs. control/baseline**
Jorge et al., 2011(16)	IRS-1 expression	↑65% IG		p<0.05
Castaneda et al., 2006(18)	hSGLT3 expression	↑10.02 factor IG	↑0.10 factor Con.	p=0.03
	hSGLT3 protein levels	↑IG		
	GLUT4 expression	↑IG	↑Con.	NS
	GLUT4 protein levels	↔IG		
Wojtaszewski et al., 2005(19)	α1, β2, γ1	↑IG ↑Con-IG		p<0.01 p<0.01
	γ3	↓IG ↓Con-IG		p<0.01 p<0.01
	α2, β1, γ2a, γ2b	↔IG ↔Con-IG		
Holten et al., 2004(14)	IRS-1 protein content	↔IG ↔Con-IG		
	PI3K subunit content	↔IG ↔Con-IG		
	Insulin receptor protein content	↑21% ± 6 IG ↑19% ± 7 Con-IG		p<0.05 p<0.05
	Akt 1/2 protein content	↑12% ± 7 IG ↑ 22 ± 9% Con-IG		p<0.05 p<0.05
	GLUT4 density	↑40% IG ↑13% Con-IG		p<0.05 NS
Krisan et al., 2004(17)	IRS-1 protein conc.	↔Con-IG ↔HF-IG	Con. HF-Con.	
	IRS-1 associated PI3K activity	↑Con-IG ↑HF-IG	Con. HF-Con.	p<0.05 p<0.05
	Akt activity	↑HF-IG ↔Con-IG	HF-Con. Con.	p<0.05
	Akt 1/2 protein conc.	↔HF-IG ↔Con-IG	HF-Con. Con.	
	GLUT4 conc.	↑Con-IG ↑HF-IG	Con. HF-Con. & Con.	p<0.05 p<0.05

Table 2 continuation

Effects on inflammatory cytokines				
Ref	**Inflammatory markers**	**Intervention**	**Control**	**Intervention vs. control/baseline**
Talebi-Garakani et al., 2013(8)	hs-CRP	↓DT-IG	DC	p<0.01
	TNF-α	↓DT-IG	DC	p<0.01
	IL-6	↓DT-IG	DC & Con.	p<0.04
Jorge et al., 2011(16)	hs-CRP	↓IG		P<0.05
	TNF-α	↑IG		NS
	IL-6	↑IG		NS
	Adiponectin	↔IG		
Abd El-Kader, 2011(20)	TNF-α	↓IG		p<0.02
	IL-6	↓IG		p<0.03
Effects on lipid levels and oxidative metabolism				
Ref	**Lipids and genes**	**Intervention**	**Control**	**Intervention vs. control/baseline**
Bittel et al., 2020(15)	TG conc.	↓IG	Con.	p=0.01
	TRL-TG conc.	↓IG	Con.	p=0.01
	VLDL-TG conc.	↔IG	Con.	
	NEFA conc.	↔IG	Con.	
	Lipid oxidation rate	↑IG	Con.	p<0.05
	Adipose tissue gene expression: FOXO1, LPL & ADIPOQ	↑IG	Con.	p<0.05
	Skeletal muscle gene expression: FOXO1 LPL	↑IG ↑IG	Con. Con.	p<0.04 NS
Jorge et al., 2011(16)	TGL	↓IG		p<0.05

↑:*Increase,****↓:****Decrease,* ***↔:****No alteration/difference,* ***p:****p-value,* ***IRS-1:****Insulin receptor substrate 1,* ***IG:****intervention group,* ***Con:****Control,* ***Conc:****Concentration,* ***NS:*** *not significant,* ***Sed:****sedentary,* ***DT:****diabetic trained,* ***DC:****diabetic control,* ***HF:****High-fat,* ***hSGLT3:****Human sodium/glucose transporter type 3,* ***GLUT4:****Glucose transporter type 4,* ***α1, α2,β1,β2,γ1,γ2α,γ2β,γ3:****AMPK subunits,* ***AKT/PKB:****Protein kinase B,* ***PI3K:****Phosphatidylinositol 3-kinases,* ***hs-CRP:*** *high sensitivity C-reactive protein,* ***TNF-α:****Tumor necrosis factor-α,* ***IL-6:****Interleukin 6,* ***TG:****Triglyceride,* ***TRL-TG:****Triglyceride-rich lipoprotein-TG,* ***VLDL-TG:****Very-low-density lipoprotein-TG,* ***TGL:****Triglyceride Lipase,* ***NEFA:****Non-esterified fatty acid,* ***FOXO1:****Forkhead box protein O1,* ***LPL:*** *Lipoprotein lipase,* ***ADIPOQ:****Adiponectin, C1Q and collagen domain containing.*

4.0 DISCUSSION

The aim of the literature study was to review the molecular and cellular mechanisms underlying the effect of RT as a therapeutic and preventive intervention for T2DM pathophysiology. Compelling evidence suggests mechanistic alterations in insulin signaling molecules, release of inflammatory markers, lipid levels, and fat oxidation are affected by RT. Alterations in these mechanisms may potentiate the improved insulin signaling and glucose uptake seen in type 2 diabetics after RT.

4.1 – RT AND ALTERATIONS IN INSULIN SIGNALING AND GLUCOSE UPTAKE RELATED MOLECULES

GLUT4 expression and translocation is known to be affected by ET (4), by enhanced function of the insulin signaling cascade. This includes higher phosphorylation of the insulin receptor and IRS-1, as well as improved function of PI3K and Akt/PKB (4). These mechanisms even appear as acute effects of ET (4). Ultimately, these are alterations inducing increased glucose uptake in both healthy and diabetic individuals (4). However, contrary evidence exists with studies showing no effect of ET on IRS-1 and Akt/PKB (4). In addition, intensity and duration of ET seem to have an effect, where briefer and lower intensity RT may be insufficient in this regard (4). AMP-activated protein kinase (AMPK), an enzyme related to cellular stress and energy demand (4,5), appears as another candidate in exercise-induced improvement in glucose uptake (7). The AMPK signaling cascade may be activated following muscle contraction (4,7), potentiating both GLUT4 expression and translocation as an insulin-independent mechanism facilitating glucose uptake during exercise (5). Increased expression of AMPK subunits α1 and α2 as well as AMPK activation, has been shown to follow ET in general, and RT specifically (4). However, ET-induced alterations in AMPK are not consistent in all studies (4).

Krisan et al. (17) demonstrated RT induced up-regulation of insulin stimulated IRS-1 associated PI3K activity in quadriceps muscle of rats, both in RT controls (con-IG) and intervention group (HF-IG) (table 2). The observed increase in GLUT4 concentrations may be resultant of the increased IRS-1 associated PI3K activity (5). Of note, the high fat (HF) diet used to induce diabetic conditions in this study negatively affected Akt, GLUT4, and IRS-1 associated PI3K activity, with RT reversing some of these signaling deficits. In compliance with these findings, Jorge et al. (16) showed an 65% increase in IRS-1 expression in IG subjects. However, results regarding IRS-1 and

PI3K were not consistent in all cases (table 2). Despite improvements in IRS-1 associated PI3K activity, Krisan et al. (17) did not reverse HF-induced deficits in IRS-1 protein concentration. Additionally, Holten et al. (14) did not observe any alterations in protein content of IRS-1 and PI3K, in either T2DM (IG) and control subjects (con-IG). To be noted, only the p85 subunit of PI3K was investigated (14), thusly not clarifying the effects on total PI3K or other possible subunits. Collectively, these results may point towards enhanced activity of these proteins, with RT to a lesser degree influencing the amount available during signaling.

Nevertheless, Holten et al. (14) demonstrated increased GLUT4 density. Healthy control subjects (Con-IG) also showed an increase in GLUT4 density, although insignificant when compared to baseline values. Concerning how T2DM might disrupt GLUT4 function (4), diabetics may perhaps obtain a greater RT-induced effect of alterations in GLUT4 properties compared to healthy individuals. In addition, both groups demonstrated an increase in insulin receptor content. A larger increase was also seen among diabetics compared to controls in this parameter, however the authors did not note if this difference was significant between the groups. Contrary to the possibility of diabetics being more prone to such positive alterations, the increase in Akt 1/2 was higher in Con-IG. As with the insulin receptor, no marks on the significance in this difference was given. In Krisan et al. (17), only subjects with muscle IR from HF diets had elevations in Akt activity after training, this compared to HF controls. This normalized Akt activity in the HF-IG compared to both control groups, with no further elevations seen in either the HF-IG or Con-IG with training. Again, this points to higher susceptibility amongst diabetics to such effects. To be noted, contrary to Holten et al. (14), the Akt 1/2 concentration was unaltered after training in both RT groups compared to respective controls (17). However, both HF-IG and Con-IG showed increases in GLUT4 concentrations. Interestingly the HF-IG showed significant elevations of GLUT4 concentrations even compared to healthy controls, pointing to improvements induced by RT beyond that of normal healthy function in sedentary conditions (17). Despite alterations in GLUT4 properties being a major candidate for RT-induced T2DM improvements, Castaneda et al. (18) did not note any significant difference in GLUT4 expression in T2DM subjects following RT compared to controls. Additionally, no alteration in GLUT4 protein levels were observed compared to the baseline. However, only a subset of 5 subjects were tested for this parameter.

Increased expression of AMPK subunits was observed in Wojtaszewski et al. (19). This outcome was higher amongst diabetic subjects compared with exercising controls, although not specified if significant. However, the increase seen in insulin sensitivity in this study was not correlated with AMPK protein content (19). This may imply other mechanisms at play affecting insulin signaling and glucose uptake rather than AMPK. Some subunits did not alter, and some decreased (table 2), which otherwise could explain the lack of correlation. In addition, this raises the question if AMPK function in relation to glucose uptake is dependent on subunit specificity (19). Interestingly, Castaneda et al. (18) points to RT-induced changes in glucose transport independent of both insulin and AMPK, as well as GLUT4. In fact, sodium-dependent D-glucose co-transporters (SGLT) expressed in skeletal muscle facilitates this process. The study showed increased SGLT3 transcripts and hSGLT3 protein after RT (18). Improvements in glycemic control in type 2 diabetics in this study may have been associated with alterations in the SGLT3 transporter system.

As outlined above, key molecules involved in insulin signaling seem to be affected by RT. Consequently, RT may restore dysfunctional insulin signaling by affecting these mechanisms. Increased expression and translocation of GLUT4 leading to higher densities and concentrations, and perhaps even alterations in SGLT proteins emerge as culminations of these processes. Therefore, these appear as mechanistic contributors to improving glucose uptake, especially in subjects with existing dysfunctions in the related mechanisms following RT.

4.2 – RT AND ALTERATIONS IN INFLAMMATION

As stated earlier, obesity is a major factor increasing the risk for T2DM (1,3), especially regarding its effect on inflammation (4,6,9–11). Despite its implications on the mechanisms described earlier, some debate exists regarding TNF-α and its involvement in T2DM, due to cases where TNF-α is not elevated in diabetics (10). IL-6 is another suspect involved in metabolic conditions such as T2DM (9). High levels of IL-6 are a characteristic observed in type 2 diabetics and obese individuals (4,9). However, to what capacity IL-6 contributes to its pathophysiology is unclear (4,9,10). IL-6 is nonetheless believed to cause IR, down regulating GLUT4 and IRS-1 expression, in addition to blocking PI3K (4). Particularly, chronically elevated levels of IL-6 is associated with the diabetic state of obese and T2DM individuals (10). Increased hs-CRP may also exacerbate T2DM complications and cause IR (10). Adiponectin however, an anti-inflammatory and insulin

sensitizing adipokine (6), is believed to act positively on fatty acid oxidation and glucose uptake (4), in part by AMPK activation (4). However, type 2 diabetics exhibit lower levels of adiponectin, associating it with IR and T2DM (4).

ET is known to reduce inflammation (4). However, acute exercise has in some cases been shown to not alter TNF-α expression, and in some instances increases in cytokines may be seen as an effect of muscle damage following ET (4). Some studies are inconclusive in determining ET and its effects on TNF-α, sometimes depending on exercise modality, intensity, and duration (4). However, lowering of TNF-α levels appear as an effect generally potentiated by RT and ET, even without fat loss (4). Increases in IL-6 have been observed following exercise (4,9) and may even be involved in anti-inflammatory processes improving glucose uptake acutely after RT (4). Hence, increased IL-6 acutely during and after exercise appear as a mitigator for T2DM complications. Chronically elevated levels, however, may be disruptive, and IL-6 levels have been shown to decrease as a long-term effect of exercise (4). Still, how exercise influences the IL-6-T2DM relationship is somewhat complex and controversial (4,9). RT has also been shown to not induce improvements in IL-6 levels (10). Decreased hs-CRP levels have also been reported following ET (6). In addition, adiponectin may be increased after ET, with results showing alterations to be in some cases independent of modality, affected by intensity or duration, or dependent on obesity status and if weight loss follows ET or not (4).

Two of the studies presented in table 2 showed a significant reductions in TNF-α after RT (8,20). Long-term RT was shown to significantly reduce IL-6 levels in obese and diabetic individuals, in Abd El-Kader (20) compared to baseline and in Talebi-Garakani et al. (8) compared to controls. The latter one even compared to healthy controls. Based on the T2DM-inflammation relationship presented above, reductions in TNF-α and IL-6 may be contributing positively to T2DM complications. Abd El-Kader (20) noted decreases in IR, possibly as a consequence of inflammation reduction. Lack of equivalent reduction in IR markers in Talebi-Garakani et al. (8) may be a result of the pancreatic damage after streptozotocin injection, hence reduced secretion of insulin. Contrary to these studies, Jorge et al. (16) showed increases compared to baseline of both TNF-α and IL-6 in the RT group, however not significant. In addition, no alterations in adiponectin were present. Despite insignificantly altered TNF-α, IL-6, and adiponectin levels, the study did

note increased insulin sensitivity in trained subjects (16). If in any relation to inflammation, this could be explained by the observed reductions in hs-CRP. However, reduction in this marker was also observed in non-exercising controls (not shown in table 2) (16). Importantly, this study examined alterations in other parameters (discussed in 4.1 and 4.3), which could otherwise explain the increased insulin sensitivity. Talebi-Garakani et al. (8) also noted reductions in hs-CRP after RT. Contrary to Jorge et al. (16), this reduction was significant compared to non-exercising controls.

Based on the findings from the articles mentioned, RT seems to affect inflammation in diabetics, however, inconclusive to what degree and specificity of function in relation to the factors involved. Despite the fact that inflammatory reduction may transpire without weight loss (4,6), exercise induced reduction in abdominal adiposity could otherwise indirectly reduce inflammation (9). Reduction in the discussed inflammatory markers is nonetheless believed to be involved in restoring adequate insulin signaling and glucose uptake.

4.3 – RT AND ALTERATIONS IN LIPID LEVELS AND OXIDATIVE METABOLISM OF ADIPOSE TISSUE

In addition to its effects on inflammation and reduced adiponectin, obesity in relation to T2DM is characterized by elevated levels of lipids impairing insulin signaling (11). IR in adipose tissue hinders insulin's role in inhibition of lipolysis, culminating in excess lipids in the blood plasma (6). This may potentially lead to shifts in location of triglyceride (TG) synthesis, most notably to skeletal muscle, contributing to the reduced muscle insulin sensitivity seen in T2DM (11).

Skeletal muscle is a key contributor of lipid disposal (22). Fitting to this description, RT has been shown to favorably improve the lipid parameters associated with obesity and T2DM (22). Among these are lipoproteins and TG, even without changes in diet and weight (22). However, limitations to these claims exist. One meta-analysis did note improved outcomes of the T2DM-related Glycated hemoglobin marker following RT. However, no significant improvements in TG or lipoprotein levels were established in correlation with these improvements (22).

Studies presented in table 2 show potential RT improvements on lipids. Bittel et al. (15) showed that acute RT prior to food consumption significantly reduced both the endogenous and exogenous lipemic response. Decreased TG and Triglyceride-rich lipoprotein-TG (TRL-TG) levels were established compared to control condition. RT may thusly mitigate the dysfunctional lipid regulation seen in type 2 diabetics. Similarly, Jorge et al. (16) also points to altered lipid profile after RT, through decreased Triglyceride Lipase (TGL). TGL is an enzyme catabolizing fat, and when stimulated increases the release of fatty acids (6). However, decreases were also present in controls (not shown in table 2). The study reported improved insulin sensitivity in trained subjects. If this is not due to decreased TGL, it could be explained by the other mechanisms examined in the study (discussed in 4.1 and 4.2). No alterations in Very-low-density lipoprotein-TG (VLDL-TG) or Non-esterified fatty acid/free fatty acid (NEFA/FFA) concentrations were seen compared to controls in Bittel et al. (15). Moreover, this study demonstrated increased expression of several genes involved in lipid oxidation and metabolism (table 2). Improvements in whole-body lipid oxidation, importantly including skeletal muscle, were observed following alterations in this expression pattern (15). Forkhead box protein O1 (FOXO1) appears as one of these gene candidates, a gene implicated in lipid mobilization, glucose sparing and inhibition of lipid storage (15). Lipoprotein lipase (LPL) expression also increased in both tissues examined, however not significantly compared to controls in skeletal muscle. LPL facilitates lipid clearance, potentially explaining the decreased TG and TRL-TG, and may additionally indicate improved insulin function (11). In addition, increases in expression of adiponectin (ADIPOQ) were observed. As discussed in 4.2, this protein is involved in regulation of glucose metabolism and breakdown of fatty acids. As noted in 4.2, Jorge et al. (16) did not observe alterations in adiponectin. The increased ADIPOQ expression seen in Bittel et al. (15) could possibly contrast these results. This may support the understanding of adiponectin as a contributor in ET induced T2DM improvements (4), hence appearing as a potential candidate in this study involved in improved lipid regulation.

Collectively, these results provide an insight to how RT may mitigate T2DM related pathophysiology, via blood plasma fatty acid utilization as well as by processes regulating body fat. In addition, reductions in TG and LPL activity might function as a proxy for improved insulin function (11). These processes may thus be involved in restoring normal glucose uptake and insulin signaling as a favorable aspect of RT in treatment and prevention of T2DM.

4.4 – METHODOLOGICAL LIMITATIONS

Limitations may be present, both in this literature study and the studies included. Regarding how results from animal models extrapolate to human conditions, relevant in two of the included studies (8,17), may not be a limiting factor (23). Genetic, physiological, and anatomical similarities to humans do not limit their utility in studying disorders like T2DM (23). Furthermore, the sample size in the included studies is relatively small, ranging from 10-32 subjects (table 1). The number of subjects can be an important factor, as larger sample sizes provide more reliable estimates and less uncertainties about their results (16,24). The subjects in the studies varied in treatment and diabetic conditions (table 1), and it is therefore uncertain whether the results can be generalized for other patient groups, hence affecting their external validity (24). In Bittel et al. (15), the subjects were prediabetic, followed no recommended diet, and did not use insulin or other blood glucose lowering medications. These conditions contrast with the subjects in the other human studies (14,16,18–20), where participants in the intervention groups were diagnosed with T2DM (table 1). Additionally, dietary recommendations were given to the subjects in Holten et al. (14) and Wojtaszewski et al. (19). Medications were also used by 6 subjects, as did the subjects in Jorge et al. (16). Comparing these studies collectively as done in 4.1, 4.2 and 4.3, despite variations among them potentially affecting these comparisons, may appear as a limitation in this literature study. In general however, randomized control trials, such as the included studies (table 1), can have high internal validity due to randomization and the defined inclusion- and exclusion criteria (24). Thusly, the subject characterization is not necessarily a limitation in each study individually.

Furthermore, results presented and discussed are based on studies possibly examining only a few parameters. Cytokines like IL-8, IL-1β and IL-10 might be affected by exercise (4). However, none of the studies presented in table 2 reported on these cytokines. The specificity of the literature search may have contributed to such limitations. Additionally, subsets of the effector mechanisms were in most part investigated separately in these studies. Some of the beneficial effects on insulin signaling described in 4.1, could possibly be mediated by the effects of RT highlighted in 4.2 and 4.3. However, inflammation, lipids and fat oxidation were not aspects of interest in these studies. Hence, they may only reflect smaller specific parts of the larger overall mechanism. Furthermore, several results from the studies were excluded, due to limitations in finding support in the literature regarding them as major contextual contributors in the mechanisms discussed. Mainly protein

kinase C in Krisan et al. (17), Glycogen synthase in Holten et al. (14) and several genes in Bittel et al. (15) were excluded by this decision. Because of these limitations, the complete picture of RT induced alterations improving T2DM pathophysiology may not be present.

Improvements in glucose uptake and IR following RT may be time dependent, where chronically trained show optimal improvements between 16-48 hours post exercise and acutely trained only between 12-24 hours (12). The discussed mechanisms may be activated at the same time-dependent manner. Results presented in table 2 may thusly have been affected by at which time measurements were taken, and therefore affect the validity of the results. This could possibly explain why Castaneda et al. (18) did not observe increases in GLUT4 expression and protein levels 72 hours post RT, while Holten et al. (14) demonstrated a 40% increase in the same parameter at 16 hours. Interestingly, Jorge et al. (16) measured the increased IRS-1 expression one day post training, and noted a decrease 5 days later, also pointing to time dependent activation. However, IRS-1 protein content was not altered after 16 hours in Holten et al. (14), perhaps indicating the time pattern in expression of this molecule being slower. Abd El-Kader (20) did not report time of measurement post RT, and Bittel et al. (15) measured only 30 minutes after RT. Both studies showed improvements in parameters related to mechanisms positively affecting T2DM.

As discussed, the mechanisms of interest may be affected by exercise intensity and duration. The included articles did not use identical RT protocols (table 1). This may have weakened the results due to limiting the possibility to establish similar effects on the same systems of mechanisms. Additionally, data extracted from muscle was obtained from vastus lateralis in 5 studies (14–16,18,19). Krisan et al. (17) also investigated the quadriceps (unspecified which part), with the addition of the gastrocnemius. Results from the gastrocnemius were excluded in the present literature study, with respect to a reliable coherence regarding vastus lateralis/quadriceps. To be noted however, results from gastrocnemius did only deviate from that of quadriceps when comparing GLUT4 concentrations between HF-IG and Con (table 2). Nonetheless, results may not reflect how RT impacts glucose uptake molecules in other muscles. Which raises the question if RT in T2DM treatment and prevention is dependent on other mechanisms than those presented, during training of other muscle groups.

In closing, due to the aim of this literature study, results regarding improved IR or T2DM are not to the same degree elaborated upon, but rather with a focus on the proposed mechanistic pathways behind these effects. One could argue that a larger inclusion of correlations between mechanism and T2DM outcomes might be important in determining these mechanisms to have this effect. In this regard, the aim of this literature study might present itself with an inherent limitation. However, based on the literature used in conjugation with the results, the mechanisms presented and discussed appear as partly responsible for the positive effects of RT in T2DM treatment and prevention. Nevertheless, it should be taken in to consideration that this subject remains to be fully understood (3,4).

5.0 CONCLUSION

Dysregulated lipid levels and inflammation appear as culprits in insulin signaling cascade disruption, ultimately reducing GLUT4 mediated glucose uptake as an apotheosis in T2DM pathophysiology. According to the results presented in this literature study, several mechanisms may be implicated in how RT counteracts these disruptions, and hence functions as a therapeutic and preventative intervention for T2DM. Increases in GLUT4 expression, translocation, density, and concentration, mitigated by alterations in AMPK, PI3K, IRS-1, and Akt/PKB appear as direct effects of RT. Some of these mechanisms even appear as functioning independent of insulin, advantageous regarding the IR state associated with T2DM. In addition, RT may reduce levels of inflammatory markers, fatty acids, and lipids through enhanced clearance and oxidation. Alterations in these mechanisms may potentially be involved in restoring proper insulin signaling and glucose uptake.

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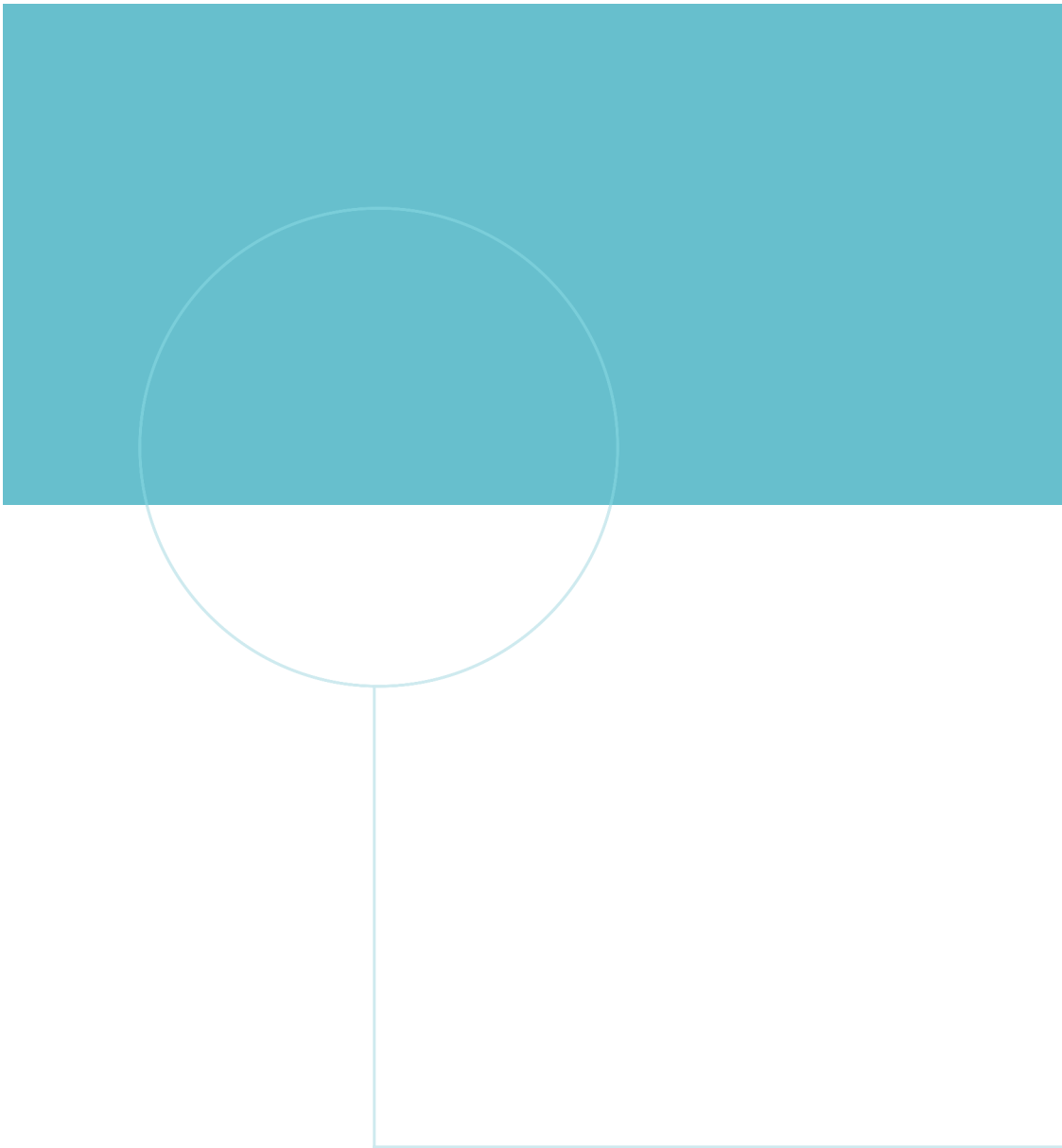

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