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Abbreviations: T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; IR, insulin resistance; FAM, family with sequence similarity genes; α7nAChR, nicotinic acetylcholine receptor α7 subunit; HFD, high-fat diet; WT, wild type; KO, knockout; TNF, tumor necrosis factor; NF-κB, nuclear-factor κB; STING, stimulator of interferon genes; IRF3, interferon regulatory factor 3; OR, odds ratio; AGEs, advanced glycation end-products; sRAGE, soluble receptor for AGEs; GDM, gestational diabetes mellitus; AI, augmentation index; HRV, heart rate variability; CAN, cardiovascular autonomic neuropathy; miRNAs, circulating microRNAs; OSA, Obstructive sleep apnea; MAI, micro arousal index; HOMA, homeostasis model assessment index; SF, sleep fragmentation; IH, intermittent hypoxia; SFA, saturated fatty acids; MetS, metabolic syndrome; WAT, white adipose tissue; ASCs, adipose-tissue derived mesenchymal stem cells; BMI, body mass index; CHD, coronary heart disease; ATMs, adipose tissue macrophages; VANAS, Veterans Affairs Normative Aging Study; SCFAs, short-chain fatty acids; PLA, placebo; INU, inulin; AC, arcuate nucleus; TGF, tumor Growth Factor; hs-CRP, high-sensitivity C-reactive protein; FFAs, free-fatty acids; TG, triacylglycerol; ApoJ, apolipoprotein J; TET, ten-eleven translocation; PPAR, peroxisome proliferator-activated receptor; NEFA, non-esterified fatty acids; ISG, interferon stimulated genes; LPS, lipopolysaccharides; MyD88, myeloid differentiation primary response gene 88; SM, skeletal muscle; IDE, insulin-degrading enzyme; AFI, activins-follistatins-inhibins; OEA, Oleoylethanolamide; GLP-1, glucagon-like peptide 1; FDA, food and drug administration; EE, energy expenditure; RDS, renal dopaminergic system; FO, fructose-overload; IL, interleukin; RAS<, renin-angiotensin system; RDS, dopaminergic system (RDS); PCOS, polycystic ovary syndrome; PCR, polymerase chain reaction; MPS, myocardial perfusion scintigraphy; CAD, coronary artery disease; MICT, moderate intensity continuous exercise training; HIIT, high-intensity interval exercise training; NASH, nonalcoholic steatohepatitis; WG, whole-grain; RG, refined-grain; mTOR-SREBP1-FAS, mechanistic target of rapamycin-sterol regulatory-binding protein 1 – FAS; METIT, Metabolism of Disease with Isotope Tracers trial; AMPK, AMP-activated protein kinase; CREB, cAMP response element-binding protein; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator1alpha; PYY, peptide YY.

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1. Introduction

Metabolism has published a lot of exceptional work within this ever-expanding field during the past year. Here, we present the most notable articles from both basic and clinical research, which were published in *Metabolism* in 2018. This overview highlights articles across metabolic disorders, including type 2 diabetes mellitus (T2DM)/insulin resistance (IR), non-alcoholic fatty liver disease (NAFLD), and obesity, all of which have become major health problems in modern society. These manuscripts reveal novel mechanisms of the aforementioned prevalent diseases and suggest novel targets for future therapeutics.

2. Obesity

Obesity is a growing health problem, affecting approximately a third of adults in the United States and other developed countries. As obesity frequently leads to metabolic dysfunction, including cardiovascular disease (CVD), T2DM/IR, NAFLD, and cancer, research into this area is absolutely critical to developing more effective treatments.

2.1. Alleviation of Body-weight Gain in Obese Mice Through BDNF-mediated Activation of Mitochondrial Biogenesis

7,8-Dihydroxyflavone (7,8-DHF) contributes to the regulation of body weight in a similar manner to brain-derived neutrophilic factor (BDNF). Therefore, this small molecule is referred to as a BDNF mimetic, although the mechanisms of action have not yet been studied. Wood et al. aimed to investigate mechanisms and signaling pathways involved in weight-regulation induced by 7,8-DHF. 20-week old obese female C57/BL6 mice that were fed a HFD during 13 weeks were treated with 7,8-DHF for another 9 weeks [1]. Metabolic actions of the BDNF mimetic were also studied in cultured myotubes. Investigators discovered that 7,8-DHF treated mice resisted body weight gain via increased energy expenditure. Treatment with 7,8-DHF caused 5′ AMP-activated protein kinase-cAMP response element-binding protein-Peroxisome proliferator-activated receptor-gamma coactivator1alpha (AMPK/CREB/PGC-1α) pathway activation and subsequent increase in muscular mitochondrial content. These mice also demonstrated lower levels of plasma insulin, lipid content and blood glucose levels in skeletal muscle and increased muscular mitochondrial content through activation of AMPK/CREB/PGC-1α pathway. Taken together, 7,8-DHF treatment demonstrated the ability of partially reversing metabolic changes in obesity and could be a promising candidate for obesity treatment, but this remains to be confirmed in future studies.

2.2. TGF-β1 Down-regulation Has a Protective Effect Against Diet-induced Obesity

Consuming large amounts of dietary fats has been associated not only with increased prevalence of obesity, but also with the induction of hypothalamic inflammation and impairment of whole-body energy expenditure. HFD-fed mice have shown increased Tumor Growth Factor (TGF-β1) B1 and NF-κB signaling in neurons, although the role of TGF-β1 in this process has not yet been determined. Therefore, Mendes et al. investigated TGF-β1's role in regulating whole-body energy homeostasis [2]. HFD-fed C57BL/6 mice were injected with ATGF-β1 inhibitory lentiviral shRNA in the arcuate nucleus. These mice showed no changes in food intake or glucose homeostasis but demonstrated reduced fat accumulation and protection against HFD-induced changes to brown adipose tissue, which were associated with decreased levels of hypothalamic inflammatory marker TGF-β1. Additionally, improvements in lipid metabolism led to reduced fat accumulation in the liver. Whether TGF-β1 might be a potential candidate for obesity treatment needs further investigation.

2.3. FNDC5-mediated Activation of AMPK Pathway Protects Against Adipose Tissue Inflammation and Insulin Resistance

Obesity induces low-grade chronic inflammation via activation and mobilization of adipose tissue macrophages (ATMs), and this inflammation leads to insulin resistance. Fibronectin type III domain-containing 5 (FNDC5) has been linked to the browning of adipose tissue, and in recent studies, its overexpression ameliorated hyperlipidemia and hepatic lipid accumulation in HFD-treated mice. Xiong et al. fed male wild-type (WT) and FNDC5-knockout mice with chow or HFD for 20 weeks and compared insulin resistance, macrophage accumulation and adipose tissue inflammation in these 2 groups [3]. FNDC5 gene deficiency increased body weight/BMI which was further accompanied by enhanced AMPK inhibition, macrophage activity, M1 polarization, and insulin resistance in the HFD group. On the other hand, FNDC5 overexpression ameliorated these changes in both WT and FNDC5 KO mice. Based on these findings, FNDC5 may be considered as a therapeutic compound for obesity-related insulin resistance, but this remains to be confirmed in future studies.

2.4. Exenatide Does Not Regulate Energy Expenditure in Non-diabetic Subjects with Obesity

Glucagon-like peptide 1 (GLP-1) is an incretin secreted by L-cells in the intestinal mucosa and has been shown to act in the brain and periphery to cause effective weight loss [4–9]. GLP-1 release is stimulated by food intake and its agonist, exenatide, is the first from the incretin family approved for weight-loss therapy by the Food and Drug Administration (FDA) [10]. Basolo et al. investigated potential effects of exenatide on energy expenditure (EE) and energy intake in a single-center, randomized, double-blind, placebo-controlled trial with 80 healthy obese individuals who received either twice daily subcutaneous injections of either 10 μg exenatide or placebo [11]. Body weight was measured weekly during 5 weeks and during monthly follow-up visits up to 24 weeks. Exenatide did not affect 24-EE but decreased energy intake and body weight over the initial 5 weeks ($\beta = -0.039$ kg/week, $p = 0.02$). Over 24 weeks, there was no difference revealed in body weight ($\Delta = -1.72$ kg, 95% CI: −5.77 to 2.30, $p = 0.39$) in exenatide versus placebo groups. Thus, exenatide exhibits early impacts on energy intake which lead to weight loss but this is not sustained over the long-term. Future research should focus on the mechanisms which prevent continued weight loss in order to develop combination therapies and more effective weight loss regimens over the long-term.

2.5. The Prebiotic Inulin Has a Favorable Effect on Fat Oxidation in Overweight and Obese Men

Human gut microbiota has been associated with body weight, insulin sensitivity and glucose metabolism. The composition of the gut microbiome is influenced by prebiotics, which are non-digestible food ingredients benefitting a host's microbiome through altering bacterial species in gut. Inulin (INU) is one of the prebiotics which has been linked to reduced body weight, BMI, energy and fat intake in patients with type 2 diabetes mellitus (T2DM). Prebiotics are fermented into short-chain fatty acids (SCFAs) in gut. Based on this knowledge, the study conducted by van der Beek et al. investigated metabolic effects of INU ingestion in 14 healthy, overweight or obese men in a double-blind, randomized, placebo-controlled crossover trial [12]. Subjects were assigned a high-fat milkshake containing either 24 g INU or 24 g maltodextrin placebo (PLA) during 2 admission days with a 5-day washout before they received the opposite. While on INU, patients had significantly lower plasma glucose, insulin, and free fatty acids in the late postprandial period (all $p < 0.05$). INU ingestion did not affect plasma triglycerides, free glycerol, glucagon-like peptide 1(GLP-1), peptide YY (PYY), satiety scores or appetite. Fermentation into SCFAs was elevated after INU ingestion as observed through the continuous increase of 13C-SCFA ($p < 0.05$) and breathe 13CO2 enrichments. Altogether, this study suggests favorable effects on fat oxidation with INU in overweight and obese men. This will need to be confirmed in larger samples for longer periods of time.

3. Diabetes and Insulin Resistance

Diabetes and insulin resistance are growing at a rate similar to that of obesity and thus are increasing public health problems, leading to large healthcare cost burdens. While more and more effective medications enter the market, it is important to understand both the mechanisms which lead some individuals to develop IR and T2DM and by which effective treatments work.

3.1. Insulin-degrading Enzyme in Liver Plays an Important Role in Development of Hepatic Insulin Resistance

Insulin-degrading enzyme (IDE) is expressed in insulin-responsive and insulin-resistant cells and is known for its ability to degrade bioactive peptides including insulin and glucagon. Although the exact role of IDE in insulin catabolism and clearance is not well-characterized. Therefore, Villa-Perez et al. aimed to investigate how IDE affects insulin clearance and hepatic insulin resistance and conducted experiments with liver-specific deletion of *Ide* (L-IDE-KO) gene expression in mice [13]. The KO mice demonstrated higher fasting and post-prandial insulin-resistance levels, while the plasma membrane insulin receptor levels were approximately 30% lower in the same group. There was also a significant reduction (40%) of insulin signaling downstream proteins AKT1 and AKT2 in parallel with the up-regulation of genes involved in gluconeogenesis, such as *Pck1* and *G6pc* levels. These results will need to be confirmed in humans.

3.2. Impact of Systemic Inflammation on the Relationship Between Insulin Resistance and All-cause and Cancer-related Mortality

Insulin resistance is associated with not only T2DM, hypertension, CVD and cancers but also with all-cause mortality. In order to further define this association, Young Lee et al. assessed the role of systemic inflammation in association of IR and mortality for 166,849 healthy Koreans [14]. Subjects were divided in terms of insulin resistance by homeostatic model assessment of insulin resistance (HOMA) and high-sensitivity C-reactive protein (hs-CRP), and the groups were formed as follows: group 0, HOMA-IR <75% and hs-CRP <2.0 mg/L; group 1, HOMA-IR ≥75% and hs-CRP <2.0 mg/L; group 2, HOMA-IR <75% and hs-CRP ≥2.0 mg/L; and group 3, HOMA-IR ≥75% and hs-CRP ≥2.0 mg/L. During the follow-up period of 1,417,325 person-years, the multivariate-adjusted HRs for all-cause mortality and cardiovascular mortality adjusted for sex in groups 2 (HR 1.40; 95% CI: 1.19–1.64) and 3 (HR 1.68; 95% CI: 1.34–2.10) exceeded those from group 0. The risk of cancer-related mortality was also higher in groups 2 (95% CI: 1.18–1.86) and 3 (95% CI: 1.35–2.51). Questions were raised about inflammation vs. IR being linked to all-cause or cancer-related mortality, and this remains to be studied in the future.

3.3. Circulating Triacylglycerols Have Been Linked with Regulation of Insulin Secretion in Healthy Humans

T2DM is often a result of insufficient insulin secretion with or without insulin resistance. Free fatty acids (FFAs), triacylglycerols (TG) and adipocytokines play important roles in the development of impairments in insulin production and sensitivity. In the current study, Nowotny et al. investigated association of circulating lipids, adipocytokines and pancreatic fat with lower insulin secretion [15]. For this purpose, 73 nondiabetic controls underwent magnetic resonance imaging and 1H-magnetic resonance spectroscopy for fat distribution and content measurement in the whole body as well as in the liver and pancreas

specifically, and blood draws were performed for the measurement of TG and adipocytokines. After adjustment for age, sex and BMI, total and high-molecular-weight adiponectin negatively predicted fasting beta-cell function (BCF; $\beta = -0.403$, $p = 0.0003$ and $\beta = -0.237$, $p = 0.01$, respectively). Pancreatic fat had no correlation with BCF, while circulating TG revealed positive correlation with BCF ($\beta = 0.375$, $p < 0.0001$). Future studies will need to explore these further using prospective cohorts.

3.4. Circulating ApoJ Levels Correlate with Insulin Resistance in Humans

Identifying molecular markers of insulin resistance may help better understand the pathogenesis of T2DM and aid in the development of specific therapeutics. Apolipoprotein J (ApoJ) is a glycoprotein involved in glucose metabolism through the binding of specific mediators with important relationships to CVD risk [16–19], although its role in glucose metabolism was not yet clear. Seo et al. aimed to investigate ApoJ correlation with insulin resistance and the changes in ApoJ levels in response to the treatments with insulin-sensitizing medications such as metformin and rosiglitazone [20]. Cross-sectional experiments revealed a correlation between ApoJ levels and fasting glucose and insulin, HOMA-IR and body-mass index (BMI). Significantly increased fasting ApoJ levels (normoglycemic vs. T2DM; 100 ± 8.3 vs. 150.6 ± 8.5 AU, $p < 0.0001$) were observed in T2DM subjects, while rosiglitazone but not metformin treatment reduced ApoJ levels. Data of Seo et al. revealed a close correlation of ApoJ levels and IR, suggesting that ApoJ is a potential target for treating IR. Future studies will need to confirm and extend these findings in further clinical populations.

3.5. TET Proteins Interact with PPARγ to Aid Insulin Sensitization

DNA methylation may play an important role in the regulation of metabolism in general as well as in development of IR in adipocytes. However, whether DNA demethylase ten-eleven translocation (TET) proteins may be involved in this process is not yet known. In order to investigate the role for TETs in the regulation of adipocyte metabolic function, Bian et al. investigated expression of TET genes and proteins in adipocytes derived from chow- vs. HFD-fed C57/B16 mice qPCR and western blotting methods were used for assessment of TET gene/protein expression in fractionated adipocytes, and the effect of Tet2 gene on functionality of fully mature 3T3-L1 adipocytes with/without rosiglitazone treatment was studied [21]. Due to rosiglitazone's ability to bind to peroxisome proliferator-activated receptor (PPAR) gamma, gene expression and DNA methylation of PPARγ genes was also assessed. TET2 protein expression in adipose tissue was significantly reduced as a result of diet-induced insulin resistance but interestingly, when treated with rosiglitazone, TET2 gain-of-function was essential for insulin sensitization in adipocytes. TET2 physically interacted with PPARγ and played a pivotal role in rosiglitazone-mediated insulin sensitization. Future studies should confirm and extend these findings in clinical trials.

3.6. RNF41 Expression in Skeletal Muscle Regulates Insulin Resistance in Obese Women

In obesity, non-esterified fatty acids (NEFA) and lipopolysaccharides (LPS) induce activation of toll-like receptor (TLR) 4 which in turn contributes to development of obesity-related insulin resistance (IR). TLR4 effects are mediated through myeloid differentiation primary response gene 88 (MyD88) and the toll/interleukin-1 receptor domain. RNF41 is the E3 ubiquitin ligase which enhances expression of interferon stimulated genes (ISG). Ligase of E3 ubiquitin RNF41 activates TRIF-IFNI pathway, although its specific effects in regulation of insulin resistance has not yet been evaluated. Therefore, Breuker et al. obtained skeletal muscle (SM) biopsies from obese insulin sensitive (OIS) and obese insulin resistant (OIR) women and investigated RNF41 levels with IFNI pathway activation [22]. Expression of RNF41 and ISG was modulated by investigators in differentiated myotubes isolated from both groups of individuals in order to study potential modulations in the response of insulin. The inhibition of RNF41 expression in skeletal muscle of obese, insulin resistant women and inhibition of its expression in obese, insulin sensitive myotubes treated with palmitate impaired the insulin response, suggesting the important role RNF41 plays in insulin sensitization. Thus, RNF41 was identified as a promising candidate for treatment of insulin resistance, but this will need to be confirmed in future studies.

3.7. Changes in Cerebral Oxygenation during Exercise in Women with Gestational Diabetes

Gestational diabetes mellitus (GDM) is associated with multiple complications in women including cardio- and cerebrovascular diseases, impaired metabolism and blood flow regulation. In this cross-sectional, observational study, levels of cerebral oxygenation were evaluated in 21 pregnant women with GDM, as compared to 16 healthy, pregnant individuals (all 25–42 years old) [23]. Near-infrared spectroscopy was used to monitor changes in cerebral oxygenation during the intermittent handgrip exercise protocol. The study revealed higher augmentation index (AI), a measure of vascular function, in women with GDM. This group also showed smaller force ($p < 0.005$) and lower increase of area under the curve (AUC) in cerebral oxygenation during the exercise ($p < 0.01$). Cerebral oxygenation was significantly correlated with measures of vascular function ($p < 0.05$). Altogether, the study revealed impaired cerebral vascularization in women with GDM during exercise. Future studies are required to reveal the association of this impairment with cerebrovascular complications, which are characteristic for women with GDM, as well as impacts on future metabolic and cognitive health.

3.8. Insulin Resistance May Lead to Cardiovascular Problems

T2DM is associated with a variety of complications. 20% of people with diabetes suffer from cardiovascular autonomic neuropathy (CAN), characterized by reduced heart rate variability (HRV). In order to investigate the association of lower HRV with insulin resistance and insulin secretion in new-onset diabetes, Ziegler et al. conducted a cross-sectional study including 275 participants with type 1 and 450 participants with type 2 diabetes both of which were diagnosed during the previous year, as well as 81 glucose-tolerant controls [24]. The diabetes groups demonstrated lower insulin sensitivity (calculated as M value) and glucagon-stimulated incremental C-peptide (ΔC-peptide) levels in comparison to the controls ($p < 0.05$) after adjustments. A positive association was found in vagus-mediated HRV indices with M-value in type I and type 2 diabetes (strongest with very low frequency power [VLF] $r = 0.268$ and 0.282 respectively). Negative correlations of similar magnitude with ΔC-peptide were observed across HRV indices only in type 1 diabetes ($p < 0.05$). The authors concluded that for T2DM, insulin resistance may contribute to the development of cardiovagal suppression at earlier time points, while in type 1 diabetes, a lower glucagon-stimulated insulin secretion may be associated with compensatory higher parasympathetic tone. This will need to be confirmed by future studies.

3.9. Circulating MicroRNA Profile of Obese Children Might Be a Future Diabetes Predictor

Childhood obesity is a rapidly growing health problem worldwide. Recent studies have suggested that circulating microRNAs (miRNAs) in serum may have a diagnostic value. Cui et al. performed miRNA high-throughput sequencing in order to screen miRNAs related to obesity in childhood and evaluate their predictive value, using miRNA data from children and adults and testing the resultant miRNAs in animal studies and tissue cultures [25]. The authors first identified three

miRNAs (miR-486, miR-146b and miR-15b) with augmented expression in children with obesity and adults with T2DM. miR-486 was involved in preadypocyte proliferation and myotube glucose intolerance, while miR-146b and miR-15b were associated with the inhibition of glucose-induced insulin secretion. The study performed by Cui et al. gives an idea about these three miRNA involvement in childhood obesity and T2DM. However, in order to fully understand their contribution to these metabolic disorders, further evaluation with longitudinal studies (to confirm later disease status in the same patients) is required.

3.10. Beneficial Effects of Whole-grain Diet on Peripheral Insulin Resistance in Obese Adults

Recent epidemiological studies suggest of beneficial effects of whole-grain (WG) dietary intake on lower risk of developing T2DM. As a result, WG diet is highly recommended to those at high risk of developing T2DM, although the mechanism of action is not yet clear. Malin et al. hypothesized that positive effects of WG diet might be associated with reduction of insulin resistance, and therefore, they compared a WG diet (50 g per 1000 kcal) with an isocaloric-matched refined-grain diet (RG) in the context of a double-blind, randomized, controlled, crossover trial involving 14 obese individuals (Age, 38 ± 2 y; BMI, 34.0 ± 1.1 kg/m^2) for 8 weeks with an 8–10 week washout followed by the opposite [26]. The insulin tolerance test was combined with isotopic tracers of [6,6-2H2]-glucose and [U-13C]-glucose and indirect calorimetry. WG diet improved post-prandial glucose tolerance, peripheral insulin sensitivity and fasting oxidation of carbohydrates in comparison to the RG diet. Changes in insulin resistance were associated with the improvement in glucose tolerance ($p < 0.05$). Both of the diets reduced body fat and hepatic insulin resistance but did not affect fasting glucose levels. In conclusion, WG diet was suggested to reduce in post-prandial blood glucose levels and thus insulin resistance. This will need to be expanded and confirmed in larger trials.

4. NAFLD

A relatively new field of study has been non-alcoholic fatty liver disease (NAFLD), which is rising in prevalence alongside obesity and T2DM/IR and which is now one of the most common causes for chronic liver disease and liver transplantation [27]. As research begins to focus on pathways for NAFLD, potential treatments are being explored in rodent and soon in clinical models.

4.1. FAM3 Gene Family Is Strongly Correlated with NAFLD

FAM3B, FAM3C and FAM3D represent the Family with sequence similarity 3 (FAM3) genes and are associated with glucose and lipid metabolism regulation. Specifically, FAM3A has been shown to be reducing liver steatosis and hyperglycemia through activation of ATP-P2 receptor-Akt and AMPK pathways. Another member of this family, FAM3C is responsible for activation of HSF1-CaM-Akt pathway and represses the mechanistic target of rapamycin-sterol regulatory-binding protein 1 – Fas (mTOR-SREBP1-FAS pathway which leads to suppression of lipogenesis and hepatic gluconeogenesis. Expression of both of the above-mentioned genes is reduced in the liver during diabetes, while FAM3B, also known as PANDER, is increased in obese rodents and promotes lipogenesis and gluconeogenesis by suppression of the Akt and AMPK pathway. Zhang et al. reviewed available data about the FAM genes and concluded that all three molecules are strongly correlated and balanced with each other and that deviations in this balance has been linked to pathogenesis of non-alcoholic fatty liver disease [28]. Therefore, the FAM genes could be studied as a target for NAFLD and diabetes treatments.

4.2. Nicotinic Acetylcholine Receptor α7 Subunit Inhibits Inflammation in NAFLD

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases associated with various metabolic disorders such as hyperglycemia, dyslipidemia, hypertension, obesity, diabetes, insulin resistance and adipokine abnormalities. Recent studies suggest that the nicotinic acetylcholine receptor α7 subunit (α7nACHR) may play a role in liver changes during NAFLD, as it affects the vagus nerve-regulated cholinergic pathway, which is known to be anti-inflammatory. To investigate the role of α7nACHR in NAFLD, Li et al. compared α7nACHR knock-out mice (α7nAChR$^{-/-}$) to the wild type controls (WT) [29]. Mice were fed with high-fat diet (HFD) during 16 weeks. After HFD, α7nAChR$^{-/-}$ mice showed increased body weight in comparison to the WT, although there was no difference in food intake between these groups when fed a chow-diet. These knock-out mice also had higher hepatic lipid accumulation, liver steatosis, macrophage infiltration, TNF-α expression, interleukin-6 and interleukin-1beta than HFD WT mice. Authors also evaluated the activation of insulin signaling pathway after insulin injection and found out that knockout mice had inhibited phosphorylation of insulin receptor at Tyr1162/Tyr1163 site (p-IRTyr1162/Tyr1163), insulin receptor substrate-1 at Tyr612 site (p-IRS-1Tyr612) and Akt at Ser473 (p-AktSer473). In order to validate their finding, authors treated KO mice with selective agonist of α7nAChR which ameliorated changes related to NAFLD. This remains to be confirmed in humans, as a potential pathway for NAFLD.

4.3. Theacrine-Mediated Acylcarnitine Metabolism Improves Fatty-Acid Oxidation

Fatty-acid metabolism dysregulation plays an important role in development of NAFLD. Specifically, acylcarnitine regulation disorder contributes to NAFLD pathogenesis through activation of NF-κB pro-inflammatory signaling pathway. Wang et al. investigated the efficiency of theacrine, an analog for caffeine found in some teas, as a treatment for NAFLD caused by acylcarnitine metabolism disorder [30]. The study examined ApoE−/− and C57BL/6J mice fed with high-fat diet (HFD), a model for NAFLD, who were given theacrine. Liver steatosis and inflammation in the liver were inhibited with theacrine treatment. Theacrine also restored normal acylcarnitine function in HFD-fed mice through improvement of fatty-acid oxidation. In order to investigate molecular mechanisms underlying mechanisms, HepG2 and L-02 cells were also employed. These experiments demonstrated activation of mitochondrial deacetylase SIRT3 which enhanced long-chain Acyl-CoA dehydrogenase efficiency. Future studies should examine potential benefits of theacrine in humans.

4.4. STING-IRF3 Pathway Induces Metabolic Disorders in Nonalcoholic Fatty Liver Disease

NAFLD is characterized by hepatocyte injury with metabolic disorders. Stimulator of interferon genes (STING) has been shown to contribute to inflammatory reaction in early alcoholic liver disease. In order to characterize the role of the STING pathway in hepatocyte metabolism and apoptosis, Qiao et al. induced hepatocyte inflammation in C57BL/6 mice by treating them with high-fat diet (HFD) [31]. Experiments revealed upregulation of STING and its downstream factor interferon regulatory factor (IRF3) upon HFD not only in liver but also in -O2 human liver cells. On the contrary, knockdown of these genes resulted in the inhibition of fat-induced hepatic inflammation and lipid accumulation, including by changes in nuclear factor κB (NF-κB) signaling pathways and inflammatory cytokines. Importantly, STING/IRF3 knockdown enhanced glycogen storage capabilities and the synthesis of glycolysis enzymes in liver. This study indicates a potential role for the STING/IRF3

pathway in hepatic injury, but this requires further characterization, especially in humans.

4.5. Exercise Training Improves Risk of Nonalcoholic Fatty Liver Disease

NAFLD is associated with multiple metabolic disorders and its progression to nonalcoholic steatohepatitis (NASH) further increases risk of liver and cardiovascular-related mortality. Aerobic exercise is recommended as part of the NAFLD treatment strategy, although not much is known about the volume and intensity of exercise for optimal benefits. Winn et al. evaluated effects of high-intensity interval exercise training (HIIT) on lipid content in liver and compared its benefits to energy-matched moderate intensity continuous exercise training (MICT) in subjects with liver steatosis, using the following groups: 1) HIIT (4 min 80% VO2peak/3 min, 50% VO2peak), 2) MICT (55% VO2peak, ~60 min), matched for energy expenditure (~400 kcal/session) and 4) non-exercising age-matched control group [32]. There were 5 subjects in control group while 18 obese adults were randomly assigned to one of the remaining groups. Blood samples were collected for measurements of glucose, insulin c-peptide and NEFA. There were differences between groups from baseline body weight, visceral abdominal adiposity and fasting insulin concentrations were higher in in MICT group compared with HIIT group ($p < 0.05$). None of the training types affected visceral abdominal adiposity, body mass, cytokeratin 18, fetuin a or the levels of aminotransferases ($p > 0.05$), although Both HIIT and MICT reduced intrahepatic lipid content (HIIT, $-37.0 \pm 12.4\%$; MICT, $-20.1 \pm 6.6\%$, $p < 0.05$) without a difference between type of exercise. Altogether, this study suggests the equal efficacy of different intensity training on NAFLD risk and decreasing IHL. Future studies should examine the mechanisms of these benefits.

4.6. Association Between Nonalcoholic Fatty Liver Disease and Colorectal Tumors

NAFLD has been associated with various diseases, although it is not clear whether it increases the risk of colorectal tumors. In order to define the association between NAFLD and colorectal tumors, Mantovani et al. performed a meta-analysis of relevant studies between 2000 and 2017 [33]. The final analysis included eleven observational studies with 91,124 asymptomatic adults of Asian descent. 32.1% of these individuals were diagnosed NAFLD, 14,911 had colorectal adenomas and 18,684 had various cancers. The meta-analysis performed by the investigators demonstrated association of NAFLD (detected either with imaging or biopsy) with a moderately increased risk of prevalent colorectal adenomas (odds ratio [OR] of 1.28) and cancer (OR 1.56) with imaging techniques, and these were independent of age, sex, smoking body mass index and diabetes. Additionally, other ethnicities should be used to confirm these associations more broadly and studies to examine potential mechanisms would be necessary. In a later meta-analysis, Perakakis et al. ruled out a possible association between NAFLD and colorectal tumors independent of age, gender, lipid metabolism, arterial blood pressure and glucose metabolism status [34]. As these studies are observational in nature, there are potentially other confounders, and thus, interventional studies to determine the links would be needed.

4.7. Elevated Levels of Advanced Glycation End-Products (AGEs) Are Associated with a High Likelihood of NAFLD

NAFLD affects 25% of the global population and its prevalence is constantly increasing. NAFLD is linked with IR, increased oxidative stress and other metabolic disorders which trigger formation of advanced glycation end-products (AGEs). Palma-Duran et al. conducted a case-control study involving 116 subjects with the purpose of investigating AGE/RAGE axis activation in liver injury [35]. 58 subjects were randomized in 2 groups – normo-glycemic with NAFLD and healthy controls. Authors evaluated the association of AGEs with liver injury at different stages of NAFLD. As expected, AGEs were 10–30% higher in patients with NAFLD. Interestingly, elevated AGEs/sRAGE ratios were associated with a high likelihood of lower transaminases ratios but a 12-fold likelihood of NAFLD presence. Future studies should confirm this data in larger samples, define these mechanisms and potentially target this pathway for NAFLD therapies.

5. Metabolic Syndrome

METS consists of various pathologies such as high blood pressure, high blood glucose, obesity, high fasting triglycerides with low levels of high-density cholesterol. The prevalence of metabolic syndrome is dramatically increasing worldwide.

5.1. Effects of Metformin on Sodium-Chloride Transporter

Metformin has been used for the treatment of type 2 diabetes mellitus (T2DM) for over 50 years. Apart from glucose-lowering effects, metformin has shown anti-aging, anti-hypertension and anti-cancer effects (REFS). In a recent study, Hashimoto et al. hypothesized that metformin might also lower blood pressure and this effect would be mediated through sodium reabsorption in kidneys [36]. To test this hypothesis, 8-week old male C57BL/6 mice were treated with metformin and urinary sodium excretion was evaluated. Short- and long-term metformin treatment inhibited phosphorylation of Na-Cl (NCC) co-transporter which in turn increased urinary sodium excretion and decreased blood pressure. NCC was the only co-transporter to demonstrate differences, as other renal sodium transporters such as NKCC2, ENaC, NHE3 showed no significant differences compared to the control mice. Which mechanisms and pathways are involved in reduction of NCC phosphorylation and whether or not this is the only change leading to lowering blood pressure as a result of metformin treatment needs further investigation and confirmation in humans.

5.2. Relationship between Obstructive Sleep Apnea and Glycometabolism

Obstructive sleep apnea (OSA) is a disorder associated with partial or complete obstruction of upper airway during sleep and is characterized by both sleep fragmentation (SF) and intermittent hypoxia (IH). Recent studies have demonstrated links between OSA and metabolic dysfunction. In order to investigate potential associations of SF and IH with dysregulated glycol-metabolism, Zou et al. enrolled 1834 subjects with OSA in a cross-sectional study and collected information about their physical measurements, polysomnographic variables and biochemical parameters [37]. Micro arousal index (MAI) and Oxygen desaturation index (ODI) were both independently associated with fasting insulin ($p < 0.001$) and homeostasis model assessment (HOMA) index ($p < 0.001$). ODI was also associated with fasting glucose ($p < 0.001$). The authors found no interactions between SF and IH on these measures, suggesting potentially separate mechanisms. Future studies should focus on interventions for OSA and/or insulin resistance to determine the directionality of these associations.

5.3. Effects of Saturated Fatty Acids on Metabolic State

Metabolic syndrome is a cluster of metabolic disorders such as obesity, impaired glucose tolerance, insulin resistance, dyslipidemia and hypertension. All of these are associated with impaired lipid metabolism. Individuals with dyslipidemia are recommended to decrease intake of saturated free fatty acids (FFAs), although there is no clear evidence that this recommendation prolongs life. Yang et al. aimed to evaluate the association between plasma saturated fatty acids (SFAs) and metabolic syndrome in Chinese adults using a case-control design of 1000 subjects with metabolic syndrome (METS) and 1000 matched healthy controls (mean age, 54.9 ± 10.7 y; 36% females) [38]. The percentage of total fatty acids in plasma of subjects was determined via

gas chromatography. Results of the trial demonstrated that different carbon numbers of SFAs have different effects on the metabolic state: even-chain SFAs (14:0, 16:0, 18:0) revealed to be associated with METS (OR: 3.32), whereas very-long chain SFAs (20:0, 21:0, 22:0, 23:0, 24:0) were inversely associated with METS (OR: 0.67). Prospective and interventional trials would be required to delve into these associations.

5.4. The Role of Acetyl-CoA-producing Enzymes in Functional Activity of Adipose-derived Multipotent Cells from Subjects with Metabolic Syndrome

White adipose tissue (WAT) as a source of various hormones and enzymes actively contributes to the metabolic homeostasis of the body. Interestingly, obese individuals with METS do not always have more visceral adipose tissue accumulation in comparison to individuals without METS. Adipose-tissue derived mesenchymal stem cells (ASCs) may be involved in remodeling of adipose tissue and development of METS. To investigate expression of acetyl-CoA-producing enzymes and their effects on adipocytes in the setting of METS, Oliva-Olivera et al. isolated ASCs from visceral and subcutaneous adipose tissue of individuals with different metabolic state [39]. Expression of acetyl-CoA-producing enzymes was decreased in adipocytes generated from visceral ASCs in METS patients. Lipogenesis, antioxidant defense and fatty acid oxidation was also lower in this group compared to the controls. Silencing of acetyl-CoA-producing enzymes in these cells resulted in a reduced lipid accumulation as shown by quantification of absorbance. No significant differences were found in percent of CD34+CD31−CD45− ASCs. According to the data presented by Oliva-Oliveira et al., adipo-subASCs may be contributing to worsening of lipogenic, antioxidative and antioxidant potential in METS, and therefore, more investigation of these effects is required.

5.5. BMI as a Marker of Adiposity in Metabolic Syndrome

In clinical practice, body-mass index (BMI) is commonly used to estimate adiposity in METS, although traditionally measures of waist circumference (WC) were preferred. Gurka et al. sought to determine whether BMI-based Z score would be more accurate than the WC-based Z score in determining METS severity [40]. To generate a METS-Z-BMI formula to calculate a BMI-based Z score, 6870 adult participants in general and in terms of sex and race/ethnicity-specific data were studied. After validation, score correlations were studied with the future development of coronary heart disease (CHD) and T2DM in 13,094 participants of Atherosclerosis Risk in Communities study and Jackson Heart Study. Despite the fact that METS-Z-BMI and METS-Z-WC have similar hazard ratios (HR), there were no significant differences between BMI- or WC-based Z scores in terms of the association with future CHD and T2DM. These data should be validated with direct measures of adiposity such as dual x-ray absorptiometry in the future.

5.6. Metabolic Phenotyping Using Kinetic Measurements

Aging is associated with changes not only in the process of cell metabolism but also in the cell mass and functionality of the tissue. Recent studies have tried to identify age-specific changes in older adults and their causes. Deutz et al. hypothesized that during the aging process, production and interconversion of amino acids is affected which leads to the observed changes related to aging [41]. Therefore, they studied 10 healthy young and 17 older adults in the MEtabolism of Disease with Isotope Tracers METIT trial. Subjects were given a mixture of stable amino acids, and whole body production (WBP) and metabolite interconversions were evaluated using GC- and LC-MS/MS methods. The study revealed similarities between groups in muscle mass, mood and cognition, while BMI was 11% higher in older adults ($p = 0.004$). Glutamine (younger vs. older: 221 ± 27 vs. 305 ± 21 μmol/kg ffm/h, $p = 0.03$) and tau-methylhistidine (0.15 ± 0.01 vs. 0.21 ± 0.02 μmol/kg ffm/h, $p = 0.04$) WBP values were significantly higher in older adults. On the contrary, arginine WBP (59 ± 4 vs. 44 ± 4 μmol/kg ffm/h, $p = 0.02$) and β-Hydroxy β-Methylbutyrate (25%; 3.5 ± 0.3 μmol/L vs. 2.6 ± 0.2 μmol/L, $p = 0.01$) WBP were reduced in older adults. Clearance rates of the amino acids, leucine, glutamine and arginine, were also increased in older adults. This data suggests that there are aging-related changes in amino acid metabolism, which require further study as to the mechanisms and metabolic consequences.

6. Other Novel Metabolic Research

6.1. The Association of Activins-Follistatins-Inhibins Axis and Energy Deprivation

Human reproduction is an energy-dependent process and conditions related to lack of energy lead to the deprivation of hypothalamic-pituitary-gonadal axis. Adipose tissue-derived hormone leptin regulates this axis in states of energy deprivation. In recent studies, follistatin and its homologous proteins have been suggested to be important players in regulation of energy expenditure and glucose regulation in healthy and obese individuals [42,43]. In the current study, the authors investigated changes in the activins-follistatins-inhibins (AFI) axis during short- and long-term energy deficiency [44]. The research performed a double-blind, placebo-controlled study with leptin treatment of healthy individuals with induced, acute energy deficiency, a case-control study of subjects with hypothalamic amenorrhea (HA) — a state of chronic energy deficiency, an open-label study of leptin treatment in women with HA during three months, and a randomized placebo-controlled interventional trial of leptin treatment in HA for nine months. Acute and chronic energy deficiency reduces levels of circulating activin A, activin B, follistatin and follistatin-like 3, and leptin treatment is not able to restore these hormones in acute energy deprivation. In long-term energy deficiency, leptin restored levels only of activin B and enhanced the number of dominant follicles. This study revealed the association between AFI axis and energy deprivation which is leptin-independent. Future research will be needed to determine the other modulators of the AFI axis and how this may alter reproduction.

6.2. The Effects of Oleoylethanolamide in Food Intake and Energy Expenditure

Oleoylethanolamide (OEA) is an endocannabinoid which contributes to the regulation of food intake. Feeding increases levels of OEA, and food restriction acts in the opposite way. Indeed, administration of OEA prolongs eating latency and reduces meal size, resulting in anorexigenic effects. These effects have been linked to PPARα. Caillon et al. studied influence of OEA on food intake and energy expenditure in control mice ((PPARα-loxP) and intestinal (Villin-Cre;PPARα-loxP) or nodose ganglion (Phox2B-Cre;PPARα-loxP) of PPARα-Knockout mice [45]. All mice had a C57BL/6 background. PPARα knockout (KO) mice showed decreased food intake, increased lipid oxidation and increased locomotor activity in comparison to the control group. On the other hand, OEA decreased energy expenditure in controls, but this reduction was not seen in KO group, suggesting that this action is conferred through PPARα. According to the results, OEA PPARα expression in intestine and nodose ganglion does not affect OEA-induced reduction of food intake, whereas PPARα presence in the intestines and nodose ganglion is essential for OEA-mediated decrease of energy expenditure. This study suggests that OEA could be an interesting candidate for clinical trials to evaluate correlations of plasma OEA levels and body fat percentage in humans.

6.3. Effects of a Combined Dietary, Exercise and Behavioral Intervention and Sympathetic System on Weight Regulation

Weight loss through lifestyle modifications is beneficial for the reduction of metabolic comorbidities in obese patients. Due to the contribution of the sympathetic nervous system (SNS) to energy homeostasis, Mai et al. aimed to investigate the potential predictive value of SNS on weight loss outputs in a 12-week long randomized controlled trial with 156 adults [46]. 143 subjects with >8% weight loss during the first phase (T0) were further randomized to a 12-month long lifestyle modification or a control group. Subjects received no intervention between month 12 (T12) and month 18 (T18) while weight regain was evaluated. 24 h urinary excretion of epinephrine and norepinephrine was measured as representatives of SNS activity. As expected, body mass index (BMI) was reduced during T0 (4.67 ± 1.47 kg/m^2) although controls during T12 regained $+0.98 \pm 1.93$ kg/m^2 ($p < 0.001$) compared to T0. Interestingly, weight regain was higher in the intervention group in comparison to the control group after lifestyle modification termination at T12 until T18 (1.17 ± 1.34 vs. 0.57 ± 0.93 kg/m^2). Urinary epinephrine excretion was predictive of BMI regain ($R^2 = 0.138$; $p < 0.05$) only during the initial changes in weight. This suggests that that other mechanisms may be at play in weight loss and regain. Future studies should investigate these mechanisms which could impact success with lifestyle interventions.

6.4. Regulation of Renal Dopaminergic and Renin Angiotensin Systems by Losartan

Renal function is regulated through the renin-angiotensin system (RAS) and renal dopaminergic system (RDS), and alterations in either of those results in hypertension. Hypertension is often comorbid with insulin resistance (IR), and this relationship has been repeatedly described in animal models of hypertension. The aim of the study conducted by Rukavina Mikusic et al. was to determine the contribution of RAS and RDS dysregulation in development of IR and if possible, to prevent this metabolic alteration via the RAS inhibitor losartan, using 96 male Sprague-Dawley rats randomly divided into control, fructose-overload (FO), losartan and FO with losartan treatment groups [47]. Mice were studied at 4, 8 and 12 weeks of treatment. FO reduced dopamine and induced L-dopa excretions and increased expression levels of angiotensin II, renal tubular Na+, K+-ATPase, pro-inflammatory (NF-kB, TNF-α, IL-6) and pro-fibrotic (TGF-β1 and collagen) markers. This increase was accompanied by microalbuminuria which is a marker of renal damage. Interestingly, losartan prevented the above-mentioned dysregulations starting at week 4, and by week 12, microalbuminuria was no longer detectable along with reduced expression of nephrin. These results should be extended and confirmed in humans.

6.5. Circulating microRNAs in Women with Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in premenopausal women. Hyperandrogenism, IR and hyperinsulinism have been identified as role players in pathogenesis of PCOS. Recent studies in patients with PCOS have suggested the importance of investigating expression of miRNAs in such patients, as miRNAs are able to induce silencing of certain gene expressions. Murri et al. aimed to characterize expression of small noncoding RNA molecules (miRNAs) in 12 patients with PCOS, 11 control women, and 12 men with similar BMI [48]. Six subjects in each group were obese. For profiling miRCURY, the LNA™ Universal RT microRNA PCR for miRNA method was utilized. Authors found a difference in expression of 38 miRNAs between not only PCOS subjects but also between male and female controls. Expression levels correlated with signs of androgenization such as hirsutism, sex hormone levels, obesity and even metabolic dysregulations. Interestingly, the expression of 15 miRNAs were similar in male controls and PCOS female subjects, but not in female controls. PCOS subjects and healthy female individuals had a similar expression pattern in 13 miRNAs, while they were not expressed in male controls, indicating the sexual dimorphism in these miRNAs. PCOS appears to be influenced by different miRNA expression which might act as a marker of PCOS. Larger studies are needed to confirm these findings.

6.6. Association Between Plasma Ceramides and Inducible Myocardial Ischemia

Ceramides are lipid molecules consisting of sphingosine and fatty acid with important structural role for the cell membrane. Ceramides are also associated with lipoprotein aggregation, cholesterol accumulation in macrophages, production of reactive oxygen species, and activation of inflammatory cytokines. In recent studies, ceramides have been suggested to predict cardiovascular events in patients with coronary artery disease (CAD), although not much is known about their involvement in stress-induced reversible myocardial ischemia. Mantovani et al. enrolled 167 subjects with CAD and measured ceramides which have been previously linked to the high-risk of cardiovascular events in human subjects before and after either exercise or dipyridamole myocardial perfusion scintigraphy (MPS) [49]. Interestingly, differences were observed between males and females in the ceramides Cer(d18:1/16:0) and Cer(d18:1/18:0) before and after exercise. Basal Cer (d18:1/24:1) levels were strongly linked with stress-induced myocardial perfusion defects (unadjusted-odds ratio 1.48 per 1-SD increment, 95% confidence interval 1.08–2.04). Ceramides were inducible in response to stress, and ceramides d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0) and Cer(d18:1/24:1) had a predictive value of stress-induced defects of myocardial perfusion. In order to evaluate the therapeutic value of plasma ceramides for CAD management, further studies are required.

6.7. Ceramide Levels in Skeletal Muscle Do Not Regulate Daily Fat Oxidation

To investigate the relationship between whole body oxidation and accumulation of ceramides in skeletal muscle, Broskey et al. measured substrate oxidation and ceramide levels in 106 study participants. Measurements revealed differences in ceramide concentrations between subjects with T2DM and controls [50]. Ceramides C18:1, C:20, C22, C24 and C24:1 were increased in T2DM, while C16 and C18 were not different between T2DM and controls. Sex, age and BMI-adjusted fat oxidation showed no differences between the groups, although fat oxidation rates were linked to the ceramide concentrations in non-diabetic controls. Thus, ceramide levels in skeletal muscle do not appear to interact with whole-body oxidation in healthy adults. This should be confirmed in larger studies.

7. Conclusions

In 2018, *Metabolism* published numerous studies uncovering the role of different mechanisms including gene and protein expression in the pathophysiology and therapy of metabolic diseases, as well as suggesting new targets and potential candidates for the therapeutic treatment. Future research should expand upon these findings to better define these disease states and identify effective therapies.

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