An Overview about Browning: Anti-Obesity Anti-Fatty Liver

Rabab Saber El. Sebaey[1], Heba H. hassan[2], Noha A.T.Abbas[3], Fawkia A. Fayed[4]

[1]Demonstrator of Clinical Pharmacology, Faculty of Medicine, Zagazig University, Egypt
[2] Lecturer of Clinical Pharmacology, Faculty of Medicine Zagazig University, Egypt
[3] Ass. Professor of Clinical Pharmacology, Faculty of Medicine Zagazig University, Egypt
[4]Professor of Clinical Pharmacology, Faculty of Medicine Zagazig University, Egypt.

Email: dr.rabab.saber93@gmail.com

Article History: Received: 11.03.2023 **Revised:**15.03.2023 **Accepted:** 17.03.2023

Abstract

Browning is conversion of white to brown-like adipocyte which is considered an attractive therapeutic strategy for the treatment of human obesity. Brown-like (Beige) adipocyte can be induced under different conditions, and this conversion is associated with decreased body weights and improving NAFLD via non-shivering thermo-genesis (NST). Accordingly, the pharmacological manipulation of browning may provide a means of influencing overall energy metabolism. There are multiple fat browning-related genes which are inducible, and their expression can be stimulated.Browning involves the expression of many transcription factors, such as PR domain containing 16 (PRDM16) and peroxisome proliferator-activated receptor (PPAR)-γ, and of uncoupling protein (UCP)-1, which is the hallmark of thermogenesis. Recent papers pointed that browning can occur in the WAT of humans, with beneficial metabolic effects. This fact indicates that these cells can be targeted to treat a range of diseases, with both pharmacological and nutritional activators. Pharmacological approaches to induce browning include the use of peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, adrenergic receptor stimulation, thyroid hormone administration, irisin and FGF21 induction. Most of them act through the induction of peroxisome proliferator-activated receptor-gamma coactivator (PGC) 1-α and the consequent mitochondrial biogenesis and UCP1 induction. About the nutritional inducers, several compounds have been described with multiple mechanisms of action. Some of these activators include specific amino acids restriction, capsaicin, bile acids, Resveratrol, and retinoic acid. Besides that, some classes of lipids, as well as many plant extracts, have also been implicated in the browning of WAT. In conclusion, the discovery of browning in human WAT opens the possibility to target the adipose tissue to fight a range of diseases. Studies have arisen showing promising results and bringing new opportunities in thermogenesis and obesity control

Keywords: Browning, Anti-obesity, Anti-Fatty liver

1. Introduction

According to World Health Organization (WHO), body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is expressed as a person's weight in kilograms divided by the square of his height in meters (kg/m2). So, Human is considered overweight when BMI greater than or equal to 25 and obese when BMI greater than or equal to 30 **(1).**

Epidemiology of obesity

Obesity has reached epidemic proportions in the past few years**.** Obesity has nearly tripled globally since 1975. Over 650 million adults (~12% prevalence) are obese. 39 million children under the age of 5 were overweight or obese in 2020 **(1).** During 2011 to 2012, more than one-third of the US population was obese. **(2)**.

The prevalence of obesity has doubled in more than 70 countries between 1980 and 2015. The prevalence of obesity is more in women than men. Egypt is the 19th highest country in the world and the 7th highest country in the Arab region, with a 32% obesity rate. At least 2.8 million people each year in the world die as a result of being overweight or obese. **(1).** Moreover, global health costs related to obesity and its complications are estimated to be about 2 trillion US$. If obesity prevalence stills on its elevating trend, almost 1/2 of the world's adult population could be obese or overweight by 2030, imposing even greater economic, social and personal costs **(2)**.

Pathogenesis of obesity:

In obesity, down regulation of caloric utilization or upregulation of appetite lead to chronic imbalance between energy intake and expenditure (EE) with subsequent storage of excess unutilized calories in form of fat (triglyceride-TGs) in adipocytes resulting in both adipocyte hypertrophy and hyperplasia. High calorie diet may be in the form of high fat, excess simple carbohydrate or industrial food with low fiber intake, and subsequently abnormal fat accumulation. Sedentary life e.g; decrease physical activity, spending hours watching television and excess use of transportation, all lead to decrease EE with subsequent abnormal fat accumulation. Excess TGs are stored lead to adipocyte hypertrophy accompanied with release of adipokines-chemokines-cytokines such as interleukins (IL-1, IL-6 and IL-8), interferon (IFN), tumor necrosis factor, leptin and resistin. These inflammatory mediators produce destruction of adipocytes inducing inflammation state in adipocyte to become chronic **(3).** So, obesity is considered a state of chronic low grade inflammation **(3).** These adipocytokines also can induce systemic affection in other organs e.g; pancreas, liver, endothelium and cognitive function**.** Oxidative stress may be a major link between obesity and its related comorbidities e.g; NAFLD, T2DM, obstructive sleep apnea and others. This may be explained by increase reactive oxygen species (ROS) Low intake of phyto-chemical rich foods such as fruits, vegetables and legumes as well as elevated circulating free fatty acids together with hyperglycemia, all are factors contributing for inadequacy of anti-oxidant defenses with the result of increase ROS and induction of oxidative stress **(4)** .

Complications of obesity:

Obesity is a risk factor for many chronic diseases, including cardiovascular disorders (as dyslipidemia, stroke and hypertension), type 2 diabetes mellitus (T2DM), infertility, osteoarthritis ,sleep apnea, dementia, non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, and an increased risk for at least 13 cancer of different anatomic sites such as esophageal, thyroid, hepatocellular carcinoma, pancreatic, endometrial, renal, postmenopausal breast, ovarian, gallbladder and colorectal cancers. Obesity is accused with worse outcomes in people with malignancy **(5).**

Elevated BMI is the 4th leading cause of risk-associated mortality, with a declined life expectancy of 5-20 years, depending on comorbidities and condition severity. Every 5-unit increase in BMI above 25 kg/m2, mortality increases by 29%, while vascular mortality by 41%, and even diabetes-related mortality by 210% **(6).**

The association between increased BMI and obesity complications are not linear. BMI does not

always reflect increased adiposity, nor does it reflect body fat distribution, which is a better predictor of obesity complications. Thus, an alternative definition, of obesity as a condition in which increased adiposity affects mental and physical health has been established. It is better to measure central adiposity, as increased waist circumference, as predicted for cardiometabolic risk, which cannot be directly peridected by elevated BMI **(6).**

The Edmonton Obesity Staging System (EOSS) takes the degree of physical and mental impairment into consideration in staging and management and is a better predictor of mortality than BMI **(7).**

Management of obesity

There are several ways to reduce weight, including pharmacological agents, however, some of them withdrawn from the market for safety concerns owing to their side effects. Other strategies were used such as; reducing energy intake (through strict diet), rising physical activity and increasing polyphenols rich food consumption (lead to great satiety, fat oxidation as well as energy expenditure). Almost, there are no pharmacological therapies that give continuous weight loss with negligible unfavorable side effects. So, many efforts have been done to reduce body weight using pharmacological treatments that possess minimal adverse effects **(8)**.

Food and Drug Administration (FDA) approved five drugs for obesity (orlistat, phentermine/ topiramate, lorcaserin, naltrexone/bupropion and liraglutide). While, the European Medicines Agency (EMA) has approved only three drug therapies (orlistat, bupropion/naltrexone and liraglutide) **(9).**

The mechanism of action of most of them is through stimulation of satiety, decrease feeling of hunger and increase catabolism. They have effect on lowering weight as well as improving metabolic parameters as blood glucose level and blood pressure **(9)**.

Surgical interventions such as endoscobic devices (e,g; balloon) or barriatric surgeries are also a treatment option for obesity. UK guidelines consider barriatric surgery when BMI ≥ 40 kgm2 or ≥35 kgm2 with obesity related commodities or when medical treatment has been failed. **(10)**. Surgical treatment attains much improvement in weight and metabolic parameters with 14-24 % weight reduction in comparison to medical treatment but has high complication rate such as anastomosis leak, anaesthesia complications, band slippage, hernia and vitamin deficiency. So, providing newer drugs are of major interest for weight loss and improving long term outcome.There is many trials to find more targets for medications to be approved by FDA and EMA to beat obesity through either lowering food intake and absorption or even enhance EE rather than lowering food intake and absorption **(11).** Some non-approved therapies for obesity e.g; glucagon like peptide-1(GLP-1) analogue, Sodium-Glucose cotransporter-2 (SGLUT-2) inhibitor, amyline mimetics, leptin analogues, gherlin antagonist vaccine, neuropeptide Y inhibitor, melanocortin-4 receptor (MC4R) agonists, cannabinoid type 1 receptor antagonist **(12)** and drugs that increase energy expenditure through stimulation of PPAR-γ dependent WAT browning **(8)**. Dapagliflozin is SGLUT-2 inhibitor which blocks SGLUT-2 in proximal convoluted tubules leading to increase urinary loss of 60-100 g of glucose (200-300 Kcal/d). It is approved for treatment of T2D and is thought to have benificial effect in obesity for both lowering weight and improving metabolic indices but also still under trials **(13)**.

Some trials to increase catabolism rather than targeting lowering food intake have been held. Converting white adipose tissue (WAT) to brown adipose tissue (BAT) for enhancing EE has been emerged as a promising option for obesity management. Rosiglitazone is an anti-diabetic drug with a PPAR-γ activity which has been widely studied for its anti-obesity effect through induction of browning and increase energy loss **(8).**

Experimental models to induce obesity in rats:

Obesity in rats can be initiated by neuroendocrine disorder (in form of lesion of ventromedial hypothalamic nucleus (VMH) through admission of monosodium glutamate (MSG) or direct electric lesion as well as ovariectomy), dietary (in form of high fat diet (HFD)) or genetic manipulation. Diet induced obesity (DIO) models are useful as weight gain can be easily initiated by this method using different obesogenic diet **(14)**

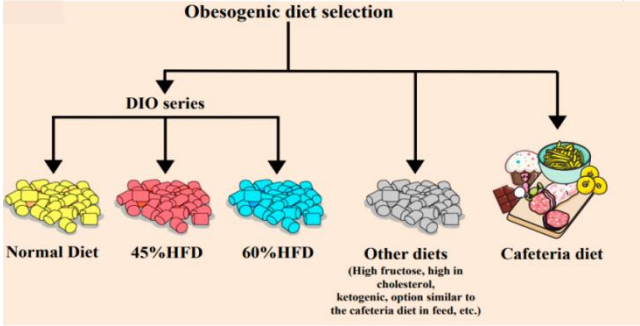

Fig (1): obesogenic diet **(15).**

Non-Alcoholic fatty-liver (NAFLD)

As regarding complications of obesity, NAFLD is considered one of the most serious complications **(2)**. NAFLD has a pathological spectrum of liver lesions that ranges from fatty liver alone to steatohepatitis, steatonecrosis, and nonalcoholic steatohepatitis (NASH). NAFLD is associated with an increase in triglycerides (TGs) in liver tissues, which causes liver damage such as steatosis, steatohepatitis, and hepatocellular necrosis **(16).**

Epidemiology of NAFLD:

Non-alcoholic fatty liver disease (NAFLD) is considered one of major health problems that results as a consequence of obesity. It affects as high as 75–100% in obese individuals, 16% of children who are overweight and 38–74% of obese children. **(17)**. Development of steatosis with

inflammation (non-alcoholic steatohepatitis (NASH)), fibrosis, and cirrhosis raised in 20% of obese individuals. If cirrhosis occurs, about 33% of patients will have bad prognosis either morbid conditions or even death **(18)**.

Pathogenesis of NAFLD in obese individuals:

The liver plays a central role in CHO, protein, and lipid metabolism, Liver can import serum-free fatty acids (FFA), synthesis, store, and export lipids and lipoproteins. However, the pathogenesis that leads to NAFLD remains unclear. The main two metabolic abnormalities most associated with NAFLD are an increased supply of FFA to the liver and insulin resistance. Consumption of high fat diet in human and rodents leads to increased plasma and tissues cholesterol as well as triacylglycerol levels, thus increases the risk of hyperlipidemia, fatty liver, and obesity. Decreased flux of fat from liver or defect in the structure and function of lipoproteins leads to accumulation of fat in the liver and subsequently hepatomegaly, changes in the shape and colors of the liver. **(19).** The equilibrium between lipogenesis and hepatic lipolysis is crucial for improvement of patients with NAFLD. In obesity, increase TGs levels is coupled with its accumulation in liver with steatosis which is a reversible process. With more fat accumulation, toxic byproducts of lipid peroxidation and oxidative stress associated with increased fat

deposition in the liver, lipotoxins and inflammation leads to steatohepatitis which is also a reversible pathology. With prolonged inflammation, death of hepatocytes with collagen deposition and fibrosis lead to cirrhosis which is irreversible **(20)**.

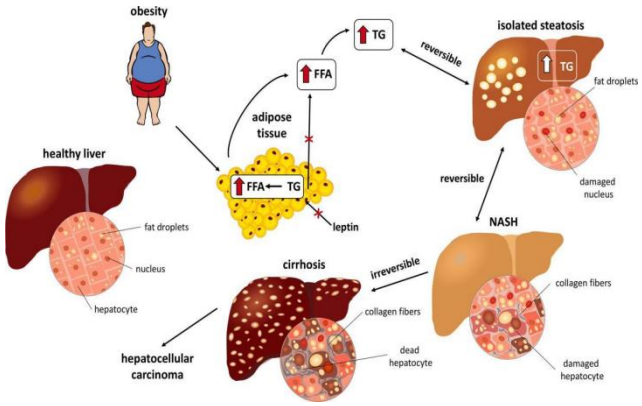

Fig (2): Obesity and fatty liver **(20)**

Browning of adipocytes:

Types of adipocytes:

Adipose tissue is a type of connective tissues. it is composed of adipocytes, preadipocytes, stromal cells, fibroblasts, and some macrophages **(21).**

In the body of an adult man there is an average of 15–20% of fat tissue, however in the body of an adult woman the value ranges from 20 to 25%. Adult human fat tissues include the known white adipose tissue (WAT) storing lipids, the transition brite (beige) adipocyte and brown adipose tissue (BAT) responsible for thermogenesis called adaptive or non-shivering thermogenesis (NST) and burning of fat in mammals. BAT is rich in mitochondria so it is metabolically active; contains uncoupling protein 1 (UCP1) which is a protein present in the inner side of mitochondrial membrane, acting through lowering the production of ATP from ADP with subsequent heat production **(22)**. So, increasing EE by induction of BAT thermogenesis is considered a promising line against obesity. NST can be stimulated by several factors e.g. cold exposure or beta 3 adrenergic receptor (ADRB3) activators that cause the beige or brown-like adipocytes to emerge within WAT depots by process called "WAT browning" **(23)**.

Adipocyte differentiation:

Adipocyte development is complex; the developmental origins of brown, beige, and white adipocytes are various. The myogenic lineage (Myf5) of mesenchymal stem cell is differentiated into brown pre-adipocyte in presence of the transcription factor early B cell factor 2 (EBF2), which subsequently differentiated into brown adipocytes through interaction with the transcriptional co-regulator PR domain containing 16 (PRDM16) with increase in expression of the thermogenic program including peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α) and UCP1, so any increase in brown adipocyte development is associated with increase in previous markers either in cells or tissue. **(25)**.

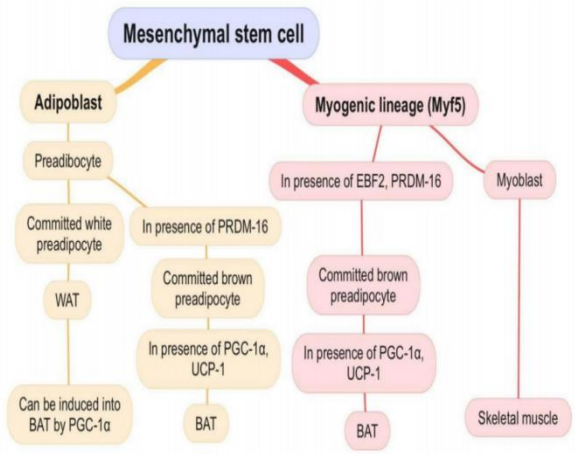

Fig (3): BAT differentiation **(26).**

Adipocyte as endocrine organ (Adipokine- Cytokine):

The perception of adipose tissue (AT) as an endocrinal organ was linked to the first discovered adipokine, leptin. Until now, many substances secreted by AT have been discovered and described. Adipose tissues store lipids as a source of energy and secretes various adipokines leading to chronic inflammation and affecting metabolism in adipose tissues and non-adipose tissues, leading to the development of various associated disorders e.g; type 2 diabetes mellitus, cardio-vascular diseases and NAFLD. Adipose tissue is an important endocrine organ in the body stores energy in the form of triglycerides and produces a variety of molecules called adipocytokines such as interleukins (IL-1, IL-6, IL-8), interferon (IFN), TNF alpha, leptin and resistin. The production of these molecules by adipocytes, coupled with the destruction of these cells, induces the inflammation to become chronic, and influences other systems by altering their functions, which leads to different diseases **(3).** Obesity is accompanied by a state of chronic low-grade inflammation. This inflammation differs from normal inflammation in that there are no typical signs of inflammation, but it is similar in that it shares the disorders generated by typical inflammation mediators and signaling pathways **(3)**. Adipocyte hypertrophy that occurs in obesity, leads to increased production of several pro-inflammatory adipokines/chemokines/cytokines by the hypertrophied adipocytes and other cells present in the adipose tissue. The increase in these molecules triggers local inflammation as well as systemic effect on other organs e.g; pancreas, liver, endothelium and cognitive function **(27).**

Browning of white adipocytes as a target for obesity management:

Browning is conversion of white to brown-like adipocyte which is considered an attractive therapeutic strategy for the treatment of human obesity. Brown-like (Beige) adipocyte can be induced under different conditions, and this conversion is associated with decreased body weights and improving NAFLD via non-shivering thermo-genesis NST. **(22)**. Accordingly, the pharmacological manipulation of browning may provide a means of influencing overall energy metabolism **(28).** There are multiple fat browning-related genes, including *Prdm16*, *UCP1*, *PGC-1α* and PPARs, which are inducible, and their expression can be stimulated. The most prominent characteristics of browning are the induction of UCP-1 expression, multiple mitochondria, and the presence of multilocular lipid droplets. Beta 3-adrenergic receptor stimulation leads to PGC1 induction through p38 mitogen-activated protein kinases (P38 MAPK) stimulation, which drives PPAR activation and mitochondrial biogenesis. These stimuli allow the white adipocyte to acquire brown adipocyte features in an event called “browning”, where the enhanced expression

of UCP1 are considered as hallmarks for thermogenic activity in the new beige/brite adipocyte **(29)**.

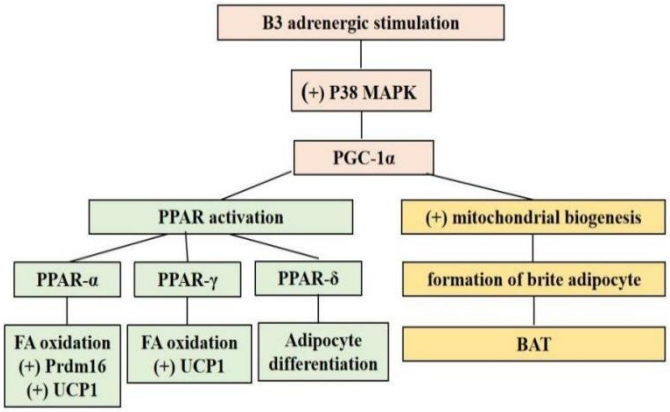

Fig (4): activation of UCP-1 **(29)**

Also, Cold exposure is known to trigger adipose tissue browning and increase M2 macrophage contents in white adipose tissues. In addition to many secretory molecules such as adiponectin, prostaglandin, and norepinephrine (NE) which are released from activated sympathetic nerve terminals are well-known stimulators of browning. Subcutaneous fat is more related to fat browning than other fats because beige adipocytes are especially abundant in the subcutaneous fat, especially the inguinal WAT. These adipocytes have clusters of UCP-1 expression with thermogenic capacity **(30)**. Like BAT, beige cells in WAT have high levels of mitochondria and express BAT specific genes, such as *UCP1* and *PGC-1α* **(8)**. Development of these thermogenic-capable cells in WAT improved resistance against metabolic diseases such as obesity **(31).** Prdm16, a transcription factor, plays a crucial role in the development of beige adipocytes. Prdm16 is abundant in subcutaneous fat and is involved in the "browning" of WAT. Mice with knock-down of Prdm16 develop obesity, insulin resistance, and increased levels of subcutaneous adipose tissues **(32).** After Prdm16-mediated browning of WAT, beige adipocytes have the ability to change from a WAT to a BAT phenotype with UCP1-containing adipocytes. In addition, Prdm16 activates brown fat differentiation in WAT preadipocytes and regulates other transcriptional factors, including UCP1 and PGC-1α by direct binding **(33)**.

Macrophage polarization and Browning of fat:

Macrophages are essential component of innate Immunity. Their infiltration into adipose tissue is a common feature of obesity. Obesity is considered a chronic low grade inflammation, so pro-inflammatory M1 macrophages play a role in obesity and its subsequent metabolic disorders **(33).** Transformation of M1 to M2 (M2 polarization) in adipose tissue leads to release of catecholamines from M2 macrophage which subsequently promotes thermogenesis via β3AR activation and subsequently stimulates browning. Several signaling pathways and transcriptional factors direct macrophage plasticity and polarization. PPARδ, PPARγ and AMPK can control macrophage polarization. Interstingly, PPARδ or PPARγ deficient macrophages have been shown to resist M2 polarization. Also, AMPK has a role activating M2 polarization **(34).**

So, induction of browning of adipose tissue may lead to increase energy loss and decrease storage of excess fat with increase fatty acid oxidation; thus preventing and treating obesity with its related complications. These effects may also exhibit anti fatty liver activity by reducing storage of excess fat in form of triglyceride in liver **(35)**

References

1. *World Health Organization. Geneva (2000): Obesity: preventing and managing the global epidemic. WHO Technical report series 894.*
2. *Ellulu M., Abed Y., Rahmat A.,et al. (2014): Epidemiology of obesity in developing countries: challenges and prevention. Global Epidemic Obesity, 2(1), 2.*
3. *Castro AM, Toledo Rojas A, Macedo de la Concha LE, et al. (2001): La obesidad infantil, un problema de salud multisistémico. Rev Med Hosp Gen Mex. 75:37---40.*
4. *Savini I., Catani M. V., Evangelista D., Gasperi V. & Avigliano L. (2013): Obesity-associated oxidative stress: strategies finalized to improve redox state. International journal of molecular sciences, 14(5), 10497-10538.*
5. *Colditz GA and Peterson LL. (2018): Obesity and cancer: evidence, impact, and future directions. Clin Chem. 2018;64(1):154-162.*
6. *Yusuf S, Hawken S, Ounpuu S, et al. (2005): Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 366(9497):1640-16499.*
7. *Sarma S., Sockalingam S., & Dash S. (2021): Obesity as a multisystem disease: Trends in obesity rates and obesity‐related complications. Diabetes, Obesity and Metabolism, 23, 3-16.*
8. *Xue Y, Xu X, Zhang X-Q, Farokhzad OC, Langer R. (2016): Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles. Proc Natl Acad Sci U S A. 113(20):5552–7.*
9. *Yumuk V, Tsigos C, Fried M et al. (2015): European guidelines for obesity management in adults. Obes Facts. 8(6):402–24.*
10. *Tolvanen L., Svensson Å., Hemmingsson E., Christenson A. and Lagerros Y. T. (2021): Perceived and preferred social support in patients experiencing weight regain after bariatric surgery—a qualitative study. Obesity Surgery, 31(3), 1256-1264.*
11. *Khera R., Murad M. H., Chandar A. K., et al. (2016): Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. Jama, 315(22), 2424-2434.*
12. *Williams DM, Nawaz A and Evans M. (2020): Drug Therapy in Obesity: A Review of Current and Emerging Treatments. Diabetes Ther. 2020 Jun;11(6):1199-1216.*
13. *Pereira MJ and Eriksson JW.(2019): Emerging role of SGLT-2 inhibitors for the treatment of obesity. Drugs. 79(3):219–30.*
14. *Avram A.S.; Avram M.M. and James W.D.(2005): Subcutaneous fat in normal and diseased states. J. Am. Acad. Dermatol. 53, 671–683.*
15. *Bastías-Pérez M., Serra D. and Herrero L. (2020): Dietary options for rodents in the study of obesity. Nutrients, 12(11), 3234.*
16. *Angulo P(2000): Nonalcoholic fatty liver disease. N Engl J Med. 346:1221–1231.*
17. *Nobili V. and Pinzani M. (2010): Paediatric non-alcoholic fatty liver disease. Gut 59, 561–564.*
18. *Hui J.M., Kench J.G., Chitturi S., Sud A., Farrell G.C., Byth K., Hall P., Khan M., George J. (2003):*

Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. Hepatology 38, 420–427.

19. *Abd Eldaim M. A., Ibrahim F. M., Orabi S. H., et al. (2018): l-Carnitine-induced amelioration of HFD-induced hepatic dysfunction is accompanied by a reduction in hepatic TNF-α and TGF-β1. Biochemistry and Cell Biology, 96(6), 713-725.*
20. *Kořínková L., Pražienková V., Černá L., et al. (2020): Pathophysiology of NAFLD and NASH in experimental models: the role of food intake regulating peptides. Frontiers in Endocrinology, 11, 916.*
21. *Lee M. W., Lee M., and Oh, K. J. (2019): Adipose tissue-derived signatures for obesity and type 2 diabetes: adipokines, batokines and microRNAs. Journal of clinical medicine, 8(6), 854.*
22. *Bartelt A. and Heeren J. (2014): Adipose tissue browning and metabolic health. Nature Reviews Endocrinology, 10(1), 24-36.*
23. *Kiefer F. W., 2017: The significance of beige and brown fat in humans. Endocrine connections, 6(5), R70-R79.*
24. *Rawish E., Nickel L., Schuster F., et al. (2020): Telmisartan prevents development of obesity and normalizes hypothalamic lipid droplets. Journal of Endocrinology, 244(1), 95-110.*
25. *Wang W and Seale P. (2016): Control of brown and beige fat development. Nat Rev Mol Cell Biol. 17:691–702.*
26. *Yao X., Shan S., Zhang Y., et al. (2011): Recent progress in the study of brown adipose tissue. Cell & bioscience, 1(1), 1-9.*
27. *Castoldi A., Nafah de Souza C., Camara N. O., et al.(2016): The macrophage switch in obesity development. Front. Immunol. 6, 637.*
28. *Bonet M. L., Oliver P. & Palou, A. (2013): Pharmacological and nutritional agents promoting browning of white adipose tissue. Biochim. Biophys. Acta 1831, 969–985.*
29. *Bargut T. C. L., Souza-Mello V., Aguila M. B.,et al.(2017): Browning of white adipose tissue: lessons from experimental models. Hormone molecular biology and clinical investigation, 31(1).*
30. *Harms M. and Seale P. (2013): Brown and beige fat: Development, function and therapeutic potential. Nat. Med. , 19, 1252–1263.*
31. *Kim S.H.and Plutzky J. (2016): Brown fat and browning for the treatment of obesity and related metabolic disorders. Diabetes Metab. J. , 40, 12–21.*
32. *Seale P., Kajimura S., Yang W., et al. (2007): Spiegelman, B.M. Transcriptional control of brown fat determination by prdm16. Cell Metab. , 6, 38–54.*
33. *Hosogai N, Fukuhara A, Oshima K, et al.(2007): Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. Diabetes. 56:901---11.*
34. *Jeon E. J., Kim D. Y., Lee N. H., et al. (2020): Telmisartan induces browning of fully differentiated white adipocytes via M2 macrophage polarization (vol 9, 1236, 2019).*
35. *Abd Eldaim M. A., Ibrahim F. M., Orabi S. H., et al. (2018): l-Carnitine-induced amelioration of HFD-induced hepatic dysfunction is accompanied by a reduction in hepatic TNF-α and TGF-β1. Biochemistry and Cell Biology, 96(6), 713-725.*