Mediating Role of Endocrine-Disrupting Chemicals in Metabolic Disorders and Their Epigenetic Effect

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Background: Endocrine-disrupting chemicals (EDCs) represent a group of chemicals which are related to the disturbances in the human hormonal system. Due to the newest research, it was discovered that their actions did not exclusively point to the hormonal system but rather to all organs of the human body. EDCs are metabolized and may excrete the influence on human metabolism. That influence can be related to the activity of different enzymes included in human metabolism. Those effects can be classified as epigenetic effects. Objective: The aim of the study was to make analysis, evaluation, examination and determination of the possible mechanisms through which EDCs may interact with different metabolically-driven diseases. Methods: This paper represents a review article that includes original and review articles that were used being published in the following databases: Medline/PubMed, ScienceDirect, Oxford Academic, and Google Scholar. Results: EDCs interact through nuclear or steroid receptors excreting their influence onto diseases such as obesity, metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD). Those mechanisms are mediated through metabolic or immunological pathways. It encompasses different types of hormones, such as vistafin or inflammatory cytokines. Conclusion: It has been noticed that EDCs may influence the appearance of specifically related diseases in offspring excreting epigenetic effects. Further research must be oriented towards potential consequences and ideal pathways for prevention and treatment options.

Keywords: Endocrine-disrupting chemicals (EDCs), NAFLD, MetS, Obesity, Epigenetics.

1. BACKGROUND

Endocrine Disrupting Chemicals (EDCs) are either artificial or naturally occurring chemicals, present in the environment (air, water and soil), drugs, food sources, personal care products, and manufactured products. So according to the definition of the EDCs, the main system that interfaces with them is the endocrine system (1). It may be included in products such as plastics due to bisphenol A (BPA) or perfluorooctanoic acid (PFOA) used in the production of non-sticking surfaces intended for e.g. non-stick pans for drying in the kitchen accessory (1).

Meanwhile, an endocrinologist Roy Hertz first claimed that the hormones being excreted through faeces may be presented in the soil and water reaching humans through a direct approach – e.g., water or indirect approach – e.g., cereal crops from affected soil (so-called food-chain) (2).

Finally, a group of scientists, gathering experts in the fields of toxicology, ecology, immunology, psychiatry and law at the Wingspread conference centre in Wisconsin (USA) in 1991; made a statement (so-called Wingspread Consensus Statement) coining a new term, which collectively covers all chemical substances capable of causing changes in the hormonal system of live beings – EDCs (1).

Throughout time, it was realized that EDCs are related to the pathogenesis of many diseases. Those diseases are metabolically caused or either malignant diseases driven by hormonal changes (2). Simply the blood is travelling all through the body as a carrier meeting with different counter mechanisms to the endocrine disruptors and eliciting many surface receptors of cells (2).

Primarily those receptors are mainly expressed on the endocrine organs but may be constitutively expressed in almost all parts of the human body mainly by acting through their interaction with nuclear receptors such as the estrogen receptors, the androgen receptor, the pregnane X receptor, the peroxisome proliferator-activated receptors (PPAR) alpha/gamma and the thyroid receptors (2, 3). Finally, nuclear receptors
are still poorly studied for their interactions with environmental ligands such as the progesterone receptor, the mineralocorticoid receptor, the glucocorticoid receptor and the aryl hydrocarbon receptor (AHR) and are suspected targets of the EDCs as well (3). After all, there is a significant influence onto the treatment course due to a further reaction with metabolizing enzymes and processes (2). There is no confirmed and defined classification of EDCs but it is possible to recapitulate as follows (1-3): a) the pharmaceuticals (trenbolone acetate, diethylstilbestrol, dexamethasone, pioglitazone / rosiglitazone, levonorgestrel) b) the personal care products (triclosan, dibutylphthalate, parabens, diethyl-meta-toluamide, benzophenones) c) the industrial chemicals (phenol – e.g., BPA, dioxins, polychlorinated biphenyls, perfluoralkyl substances, polycyclic aromatic hydrocarbons (PAH), triphenyl phosphate, phthalates) d) the agriculture chemicals (glyphosate, atrazine, organochlorides, chloryprifos, vinclozolin) e) metals – cadmium, lead, mercury, arsenic f) “inner body EDCs” representing hormones and peptides naturally produced: progesterone, testosterone, cortisol, oestrone

2. OBJECTIVE
Aims of this review article is to analyze the role of EDCs in the diseases or disorders caused using the hormonal disruption. Besides the aforementioned primary role, there is a need to evaluate the pathophysiological mechanisms of diseases related to the EDCs.

3. MATERIAL AND METHODS
The following databases are searched out applying exclusion and inclusion criteria: Medline/PubMed, ScienceDirect, Oxford Academic and Google Scholar. Evaluated keywords were searched according to the terms related to the specific groups of EDCs classified upon their characteristics due to an easier understanding and combined to terms of metabolically-mediated diseases as follows: metabolic syndrome (MetS), non-alcoholic liver disease (NAFLD) and obesity.

The inclusion criteria are as follows: available in the full English-written version, published articles as the original research papers only in peer-reviewed journals, studies including human-based population or mice-based population. The exclusion criteria are as follows: studies of non-trusted source information, studies including human-based population or mice-based population. The exclusion criteria are as follows: studies of non-trusted source information, studies including human-based population or mice-based population. The exclusion criteria are as follows: studies of non-trusted source information, studies including human-based population or mice-based population.

4. RESULTS
4.1. Metabolic Syndrome
Metabolic syndrome (MetS) represents the triad of symptoms as shown in Figure 1 as key steps towards the development of cardiovascular and endocrinological diseases through constant exposure to an inflammation on low-grade – meta-inflammation. Those patients are about to have hypertension with increased waist circumference. Most commonly, this disorder is related to diet and lifestyle.

Due to plastic-containing BPA, scientists intended to check the presence of BPA in children with obesity. Aktag et al found out that pre-pubertal obese children showed higher levels of BPA in urine, but it was significantly higher in the obese patients with a diagnosis of MetS (4). In the MetS patients, Gaston et al analyzing urinary phthalate concluded that only mono-n-butyl phthalate, as a metabolite of the dibutyl-phthalate, was present in the urine of patients related to MetS (5). Stojanoska et al researched parameters corresponding to the MetS upon an administration of the diethyl phthalate and the di(2-ethylhexyl) phthalate (6). They found out that one of a metabolite of those EDCs, the mono-2-ethylhexyl phthalate, is significantly related to the increase in components of the MetS. In vivo analysis showed that the di-(2-ethylhexyl)-phthalate acts through activation of the PPAR alpha and further activation of the constitutive androstane receptor (with its target genes) (7). Serum perfluorononanoic acid has been studied in MetS by Lin et al (8). Analyzing the parameters of MetS, they concluded that perfluorononoic acid correlates with the appearance of MetS. Huang et al analyzed the relationship between the MetS and dioxin (9). Due to the known fact that the dioxin differentially acts depending on gender, they have analyzed the male and female groups upon exposure to the polychlorinated dibenzo-p-dioxins healthy partici...
Obesity is a very well-defined cosmetic problem for millions of people who have never considered a serious pathophysiological mechanism. But in contrast, obesity has a much more intriguing appearance. From a medical side point, obesity is the status of a patient where the body mass index (being calculated by dividing a body weight and a squared body height) is greater than 30 (13). For a value in a range between 25 and 30, those patients are claimed as overweight (13). Classification of obesity according to the body mass index is arranged as shown in Figure 2. Adipose tissue is regarded as an endocrine organ that may produce hormones and adipokines that potentially influence the disease pathophysiology (14). It is ordinarily found around the peri-renal - kidney, epicardial - heart, periadventitial layer – blood vessels and subcutaneous tissue (14).

Obesity carries a different physiological status of adipose tissue. Usually, such patients have increased values of inflammatory markers such as the interleukin-6, the C-reactive protein (CRP) and the fibrinogen or angiotensin II and plasminogen activator inhibitor-1 (13). But a key relationship between the immune system and the metabolism in obesity could be a hormone with insulin-mimetic effects – vistafin, firstly discovered as the pre-B cell colony-enchaing-factor (and although being named after its function), that has a relation with proinflammatory cytokines such as interleukin-1 beta and TNF alpha (15). Also, it has been confirmed that one of the main pharmaceutical EDC – dexamethasone highly increases the value of vistafin in the population whose levels were previously in the physiological range (15). In 2013, Lee et al assessed the values of the interleukin-6 and the pre-B cell colony-enhancing factor in ventilating patients with acute respiratory distress syndrome (16). They concluded that a high value of the pre-B cell colony-enhancing factor might be a better predictor of mortality than the interleukin-6.

AHRs represent a target for many EDCs especially forbidden ones (3). Those chemicals belong to groups: polychlorinated biphenyls, PAH and heavy metals (1,3). Although the AHR is a link between the activation of PPAR gamma as it was published in 2018 by Ishihara et al showing that the AHR repressor negatively regulates the AHR through suppression of the PPAR gamma (17). On another side, there are plenty of EDCs, which act on the PPAR gamma and are shown as one of the masters for the regulation of adipogenesis and obesity (18). Schaffert et al analyzed the influence of the di-(2-ethylhexyl)-phthalate on the adipogenesis process concluding that the process of adipocytes production is related to an activation of the PPAR gamma in a pattern similar to its direct agonist rosiglitazone, previously known drug for diabetes mellitus type 2 (T2DM) (19). In the group of perfluoroalkyl substances, (PFOA) and perfluorocanosulfonates represent the two most commonly used (1). The metabolism of the EDCs gains a new perspective when two or more of those chemicals are joined together in their action – synergy. Such samples regarding adipogenesis and obesity were seen in a case of administration or exposure to the polycyclic aromatic hydrocarbons (PAH) and environmental tobacco smoke known to contain different volatile chemicals regarded as the EDCs when Kim et al conducted cross-sectional research analyzing urine metabolites of PAH with an ability of the synergetic action when being combined with the tobacco smoke in...
the obesity pathogenesis (20). Hu et al analyzed the role of parabens (ethylparaben, propylparaben, butylparaben, benzylparaben etc.) in the adipogenesis in murine 3T3-L1 cells realizing that parabens as a group of EDCs activate the glucocorticoid receptor and the PPAR gamma in 3T3-L1 preadipocytes; but later on, an activity of the glucocorticoid receptor was not shown through a maturation process and concluding that the butylparaben and benzylparaben express a strong adipogenic effect on the tested cells (21). Triphenyl phosphate is regarded as a widely used chemical due to its presence in flame retardants but more commonly in humans – in nail polishers (22). Moreover, it has been proved that nail polishers are an important source of triphenyl phosphate and easily are absorbed through nails and fingers (22). Triphenyl phosphate increases adipogenesis in 3T3-L1 adipocyte cells upon exposure via an activated transcription of the PPAR gamma (22). Adipogenic effects causing obesity were tested on multipotent murine mesenchymal stem cells by Biemann et al (23). They were tested with high and low values of mixtures of the BPA, the diethylhexylphthalate and the tributyltin. Scientists concluded that a high mixture value is an efficient obesogen and a low-value mixture is not powerful enough to cause adipogenesis and lead to obesity. Mallik et al assessed the level of urinary BPA in the North Indian children revealing that a level of more than 2 ng/mL of the fasting urinary BPA level is associated with the obese children (24). The basic pathophysiological mechanism of obesity is represented in Figure 3.

4.3. Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) encompasses a term that correlates with a liver disease developed through time so could be categorized as a chronic disorder (25). It may underlie T2DM, dyslipidemia and obesity and is increasingly recognized as a major health problem in many parts of the world and is the most commonly diagnosed in ages between 40 and 60 years (26). Maybe current statistics are not too worrying if future predictions are excluded. The global prevalence of NAFLD is estimated to be 25% and continues to rise worldwide in the setting of an obesity epidemic (26). In the United States, the prevalence is estimated to be 24% and is projected to increase from 83.1 million in 2015 to 100.9 million in 2030 (26). Financial cost is assessed at $100 billion only in the United States of America (26). It is a condition defined by the presence of steatosis in more than 5% of hepatocytes with little or no alcohol consumption (27). Classification of the NAFLD is pretty complex and meets different steps based on disease progression. It consists of the benign non-alcoholic fatty liver, and the more severe non-alcoholic steatohepatitis (25). One of the used is Matteoni’s system based on fat accumulation, inflammation, ballooning degeneration, Mallory hyaline and fibrosis as shown in Figure 4 (25). Non-alcoholic steatohepatitis is a more progressive form of NAFLD and is characterized by steatosis, hepatocellular ballooning, lobular inflammation and almost always fibrosis (26). Due to a high intensity of hepatic cell regeneration, the non-alcoholic steatohepatitis progresses to cirrhosis with the hepatocytes replaced with scar tissues of type I collagen produced by stellate cells (27). Cirrhosis presents as end-stage organ failure with concomitant shrinkage of the organ and the appearance of nodules on its surface which could either be palpated through the skin around an anatomical topographic position of the liver (25). That state requires liver transplantation or may lead to hepatocellular carcinoma. With the progression of the non-alcoholic steatohepatitis to full cirrhosis, some of the histological characteristics of the non-alcoholic steatohepatitis might be lost (25). Due to different steps in disease progression, every step carries different markers of pathophysiological profile. Foundations of the disease initiation are fatty accumulation in the liver – free fatty acids (28). The first cause could be a high-fat diet (bariatric surgery is one of the most potent ways to reduce this disease if it is applied in an early stage) although a release from adipocytes makes that predisposition in the insulin resistance (28). Very high levels of insulin may initiate the process of de novo lipogenesis (28). One of the important lipogenic stimulants is the fructose (29). The final step is the accumulation of the triglycerides together with high intrahepatic lipid levels – steatosis (27). However, there is a presumption that the accumulation of triglycerides is a tentative protective mechanism until the process of lipotoxicity (30). The enzyme in charge of the triglyceride synthesis is the acyl CoA:diacylglycerol acyltransferase 1 (31).

Knockout models of mice without the aforementioned gene were made by Villanueva et al, who found out that those kinds of mice had been protected from the development of hepatic steatosis (31). In this transition period, the triglycerides are being converted into very low-density lipoproteins (32). The next perspective which could be considered is the genetic background of patients with NAFLD. Palatin-like phospholipase domain-containing protein 3 is till now the best described in the term of this disease (33). Romeo et al identified an allele rs738409 as a target point and that was strongly associated with an increased intrahepatic inflammation and intrahepatic fat accumulation (34). Additionally, it is found that a gene – transmembrane 6 superfamily member 2 and its allele rs5842926 have a significant relation with the appearance of the NAFLD (35). Regarding the gene the membrane-bound O-acetyltransferase domain-containing 7, it is proved that it takes part in the development of NAFLD but during experiments with mice when scientists tried to reactivate this gene; the answer was that it did not influence the disease progression or regression (36). However, it has been discovered that this gene is responsible for liver fibrosis, which could be corresponding to the development of a progressive form of NAFLD (38). The immuno-
logical perspective could be a very useful particularly, due to the gene mutation leading to intrahepatic inflammation, especially if it interferes with the metabolism. Fatty acid translocase or cluster of differentiation 36 (CD36) plays a very essential role in the development of lipotoxicity (38). It is shown that NAFLD patients have an enormous level of an immunological marker, but its upregulation can be related to a high level of homocysteine (35,38). The intermittent player, which is in charge of transmitting that activation, is the AHR as was proved in mice by Yao et al (38) where the NAFLD pathogenesis is partly mediated by the increased level of homocysteine. Ohashi et al. made a paper related to the hepatitis C virus, it considered the role of the AHR intrahepatic lipid accumulation (39). It has been proved that the AHR is directly related to the activity of Cytochrome P450 1A1 under the process of intrahepatic lipid accumulation. Besides classic proinflammatory cytokines such as the TNF alpha, interleukin-1 beta and interleukin-6; the T helper cells 17 – interleukin-17 family plays an important role with their primary expression to stop the fatty acid beta-oxidation (40). Di-(2-ethylhexyl)-phthalate was analyzed by Chen et al as a cause of the NAFLD treating mice with a different daily dosage of the aforementioned EDC (0.05, 5.00, 500 mg/kg daily) and resulting in the lipid accumulation inside the liver together with the appearance of inflammation (41). AHRs take part in the development of the NAFLD by being activated by the 2,3,7,8-tetrachlorodibenzo-p-dioxin (42). For the PFOA, a role in the development of the NAFLD is mediated through autophagy in male mice (43). Weng et al conducted a research with an exposure to PFOA in 4 weeks and then sacrificed mice for analysis (43). Additionally, the human liver cell line (L-02) was used to follow the influence of PFOA revealing that the lipogenesis and the hepatic steatosis resulted in an exposure to PFOA via initiation of inflammasome NLR Family Pyrin domain Containing 3 (NLRP3), which further results in a high level of interleukin-1 beta (43). Regarding the one of most commonly used EDCs being still on the market – glyphosate (pesticide approved in EU and USA), it was found that rodents that had been chronically exposed to a low dose of the glyphosate displayed signs of hepatic steatosis with progression to necrosis (44). This long-term study was conducted in the period 2012 – 2018 at the University of California by Mills et al analyzing urine presence of the aminomethylphosphonic acid together with more expressed levels in the patients with the liver fibrosis (44). A special entity represents a hepatic steatosis or liver fibrosis caused by medicaments. It is well known that medicaments may cause liver damage leading to hepatic fibrosis with acute toxicity, such as the acetaminophen or prolonged use of the methotrexate (44, 45). Dexamethasone is a widely used corticosteroid especially due to its application in different pregnancy complications (46). Administration of dexamethasone is related to increased activity of the glucocorticoid receptors (47). Liu et al examined whether the D would be influenced by the dexamethasone administration in the offspring of the first generation (48). They found out that dexamethasone leads to increased triglyceride synthesis inside hepatocytes and even it could be continued postnatally leading to the development of NAFLD. Thereafter it is discovered that the hepatic steatosis is alleviated by decreasing the activity of glucocorticoid receptors inside the hepatocytes.

5. DISCUSSION
Analyzing the aforementioned results, it is possible to see that way of the actions of the EDCs consist of several pathways – the immunological and the metabolic leading to inflammation. Due to an altered activity of certain enzymes in charge of the metabolism, it is impossible to assess what dose is critical in some cases. The most prominent immunological parameters could be the TNF alpha and interleukin-6 (2). Further on, they could be characterized as the markers of inflammation. Regarding the metabolic pathways, they lie on several signalling pathways related to receptors: the PPAR gamma and the AHR (18,36). Thereafter, it is possible to assume that all those known parameters might give us hints and shortcuts for a better understanding of the specific disease pathophysiology and establish a future treatment. For example, we can observe that the vistatin hormone is increased in obesity but also in acute respiratory distress syndrome that represents a consequence of different diseases but the most commonly related to the SARS-CoV-2 infection in 2020 and 2021 (15, 16). Unfortunately, it was not possible to find any paper about an analysis of pre-B cell colony-enhancing factor role in the SARS CoV-2 patients and a potential comparison in patients according to their body mass index by the day of writing. An extremely important fact is that we may be exposed to certain EDCs, such as pesticides or herbicides, daily in food. But that affects genes and their activities. The first harbinger of a potential interaction between prenatal and early postnatal influence on adult disease development was given by Barker so-called “Barker’s hypothesis” (49). So a key function is how to gain-off or gain-on activity of some particular gene entering the field of epigenetics. Epigenetics is a new and very exciting field, which interferes with many disciplines of medical science. But also the appearance of transmission of an epigenetically modified gene in patients is of particular interest. First of all, in those previously listed papers it is possible to see that many of them count on consequences of the first generation; actually, some of them problematized treatment in the perinatal period. It is possible to observe changes in generation related to the inflammatory markers in the circulation of the mothers and the neonates being under EDC exposure.
Interleukin-8 and TNF alpha are found to be increased and associated with a higher infant birth weight (50). But also many compounds possess a potential epigenetic influence whose activation or increase could be caused by the EDCs such as the TNF alpha. TNF alpha intrigues inflammation due to its reactivity with the gene Runt-related transcription factor 2 in the way to increase the activity rate of CpG methylation in the rat promoter of the gene Runt-related transcription factor 2 (51). The other very well-known and widely used EDC – dexamethasone possesses an activity with the Runt-related transcription factor 2. Dexamethasone activates the aforementioned gene if it is perinatally administered and excretes its efficacy onto the following two generations (52). However, it was shown that male mice treated with dexamethasone in the prenatal period would display a decrease in the testosterone level inside the testes of mice throughout generations (53). Regarding the purpose of this previously mentioned dexamethasone role, it is related to the attenuated estradiol synthesis affecting reproduction through genetic means. The literature mentioned its target gene Runt-related transcription factor 2 as a key player in the pathophysiology of bone diseases such as craniosynososis (54).

6. CONCLUSION

Due to an altered activity of certain enzymes in charge of the EDC metabolism, it is impossible to assess what dose is critical in a case of pathogenesis. The most prominent immunological parameters could be the TNF alpha and Interleukin-6. Regarding the metabolic pathways, they lie on several signalling pathways related to receptors: the PPAR gamma and the AHR representing a clue in research of pathophysiology of EDC-caused diseases. EDCs cause changes in the offspring of the affected populations and it may represent a new diagnostic and therapeutic challenge in the future due to the widespread usage of EDCs.

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