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Modeling the Effects of Environmental Pollutants on Metabolic Syndrome in Fish

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ABSTRACT

Metabolic syndrome is a complex and multifactorial disease characterized by the coexistence of multiple metabolic disorders such as abdominal obesity, insulin resistance, hypertension, and dyslipidemia. Today, it is becoming increasingly clear that this syndrome can be triggered not only by genetic and lifestyle factors, but also by chemicals. Persistent organic pollutants, endocrine disruptors, pesticides, and heavy metals can have disruptive effects on metabolic regulatory pathways. Model organisms are critical for understanding the systematic relevance of metabolic syndrome analysis. This study will present models of the effects of environmental pollutants on metabolic syndrome factors in fish, which are aquatic organisms commonly selected to observe the effects of chemicals. As a result of applications using fish as models, biochemical and pathophysiological models of diabetes, obesity, dyslipidemia, and potentially hypertension have been provided in individuals exposed to various chemicals. In particular, zebrafish (*Danio rerio)* are preferred as model organisms in scientific studies due to their high degree of genetic and metabolic similarity to humans, transparent embryo structure, and short generation time. However, the poikilothermic nature of fish, their different metabolic response distribution, and certain genetic characteristics that are not fully compatible with humans impose limitations on the translational use of this model. In the future, it will demonstrate that recorded models obtained from fish models and human numerical systems should be evaluated holistically in order to better understand the possible consequences of such applications.

Çevresel Kirleticilerin Metabolik Sendrom Üzerine Etkilerinin Balıklarda Modellenmesi

ÖZET

Metabolik sendrom; abdominal obezite, insülin direnci, hipertansiyon ve dislipidemi gibi birden fazla metabolik bozukluğun birlikte görüldüğü karmaşık ve çok faktörlü bir hastalık tablosudur. Günümüzde bu sendromun yalnızca genetik ve yaşam tarzına bağlı etmenlerle değil, aynı zamanda kimyasallarla da tetiklenebileceği giderek daha net biçimde anlaşılmaktadır. Kalıcı organik kirleticiler, endokrin bozucular, pestisitler ve ağır metaller metabolik düzenleyici yolaklar üzerinde bozucu etkiler yaratabilmektedir. Metabolik sendrom analizinin sistematik ilişkisini anlamada model organizmalar kritik öneme sahip olmaktadır. Bu çalışma, kimyasalların etkilerini gözlemlemek için sıklıkla seçilen sucul organizmalar olan balıklar üzerinde çevresel kirleticilerin metabolik sendrom faktörlerine etkilerinin

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modellerini sunacaktır. Balıkların model olarak kullanıldığı uygulamalar sonucunda, çeşitli kimyasallara maruz bırakılan bireylerde diyabet, obezite, dislipidemi ve potansiyel olarak hipertansiyonun biyokimyasal ve fizyopatolojik modelleri sağlanmıştır. Özellikle zebra balığı (*Danio rerio*), insanla yüksek oranda genetik ve metabolik benzerlik göstermesi, şeffaf embriyo yapısı ve kısa nesil süresi gibi olumlu özellikleri nedeniyle bilimsel incelemelerde tercih edilen bir model organizma görevi almaktadır. Bununla birlikte, balıkların poikilotermik yapısı, farklı metabolik yanıt dağılımı ve insanla tam olarak uyumlu olmayan bazı genetik özellikleri, bu modellemenin translasyonel kullanımında kısıtlamalar oluşturmaktadır. Gelecekte, bu tür uygulamaların olası sonuçlarının daha sağlıklı anlaşılabilmesi için balık modellerinden elde edilen kayıtlı modeller ve insan sayısal sistemleriyle bütüncül biçimde değerlendirilmesini ortaya koyacaktır.

1. INTRODUCTION

Metabolic syndrome, which results from biochemical and physiological changes, is defined as the combination of at least three of the following metabolic disorders: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) levels, hyperglycemia (associated with insulin resistance), and hypertension [1], [2]. As a result of these changes, the risk of diseases such as chronic kidney disease, hepatic damage, myocardial infarction, and stroke increases significantly [1], [3]. First defined as “Syndrome X” by Reaven in 1988, it has since become the focus of many researchers [4]. Later, it was renamed “Metabolic Syndrome”.

In addition to risk factors such as a sedentary lifestyle and a high-calorie, regular diet, the increasing effectiveness of environmental pollutants is creating additional risk factors for metabolic syndrome [5]. Even if the individual effects of potentially risky chemical substances are within the reliable range at the measurement level, it is thought that their mixtures may be unreliable [6]. Figure 1 shows a graph from a study correlating the increase in synthetic organic chemical production with the increase in diabetes and obesity [7]. According to this pattern, the parallel between the increase in synthetic chemical production and the incidence of obesity is evident. The data suggest that exposure to chemical compounds should be considered a causal factor in the development of metabolic diseases.

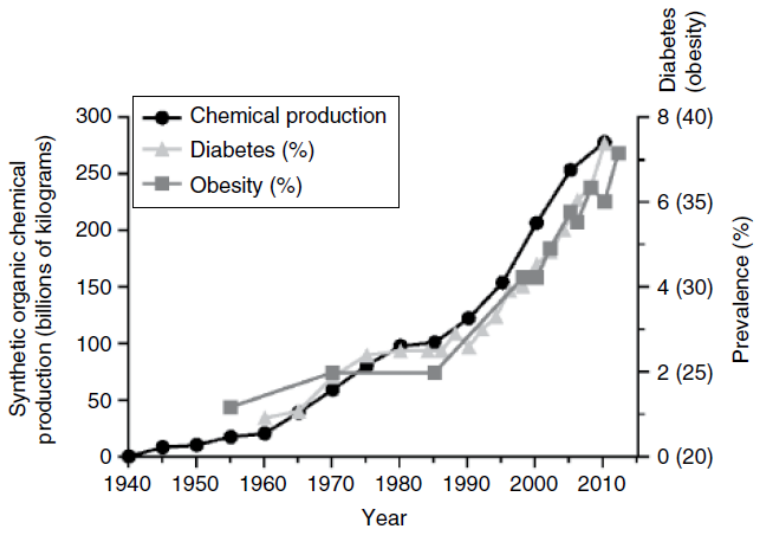

Figure 1. The increase in diabetes and obesity among the total population in the US synthetic chemical production (BMI > 30) [7]

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Fundamental research on metabolic syndrome needs to be supported by animal experiments. Fish have become important experimental animals, particularly with the threat posed by chemicals to aquatic life. In laboratory experiments, zebrafish (*Danio rerio*) may be preferred as an animal model due to their high human genetic homology, transparent embryos, and larvae. The other fish species can be preferred as indicator species during ecological observations [2].

This study details the relationship between environmental pollutants and metabolic syndrome, assesses the risk of fish developing metabolic syndrome, and provides a perspective for the future.

2. RELATIONSHIP BETWEEN METABOLIC SYNDROME AND ENVIRONMENTAL POLLUTANTS

Environmental toxins might be causing dysfunction which can be a cause of metabolic syndrome. If the disease phenotypes caused by a environmental toxin are variable among individuals. It related with its different organ specificity or different genetic background (Table 1). In particular, with the increase in anthropogenic pollutants in nature, there has also been an increase in risk factors. Some examples of anthropogenic pollutants include heavy metal pollution, persistent organic pollutants, plastic pollution, pharmaceutical pollutants, endocrine disruptors, and pesticide pollution [8].

Table 1. Brief presentation of environmental conditions, chemical diversity, mechanisms and effects.

Pollutant type	Chemicals	Mechanism	Metabolic Effect	Reference
Persistent Organic Pollutants (POPs)	DDT, PCB	Accumulation in adipose tissue, endocrine disruption	Obesity, Diabetes	[7], [10]
Endocrine Disruptors	BPA, Phthalates	Increased adipogenesis, insulin resistance	Obesity, Diabetes	[13–15]
Pesticides	Chlorpyrifos	Disruption of lipid homeostasis, hypertension	Obesity, Hypertension	[16–17]
Heavy Metals	Cd, Pb, Hg	Oxidative stress, impaired insulin signaling	Diabetes, Cardiovascular risk	[8]

Persistent organic pollutants, which are among environmental toxins, are lipophilic chemicals that can exhibit endocrine-disrupting activity, accumulate in adipose tissue, and are difficult to eliminate from the body [9]. Exposure to various persistent organic pollutants can cause obesity and diabetes, which is why persistent organic pollutants can be classified as environmental "obesogens." These chemicals have been shown to increase the amount of adipose tissue in the body, interfere with the endocrine hormone system, and affect weight control homeostasis [7], [10]. Another environmental toxin, endocrine disruptors, has been described by the World Health Organization as a "growing source of global concern" and has been noted to have effects that may extend to future generations [11]. A report published in 2015 stated that exposure to endocrine disruptors in the European Union causes obesity and diabetes, resulting in estimated annual healthcare costs exceeding €18 billion [12]. Studies on bisphenol A (BPA), which is among endocrine disruptors, have shown that it increases the risk of obesity, has a direct effect on adipogenesis,

and induces the development of insulin resistance in living organisms [13], [14] Similarly, phthalates have been found to increase the risk of obesity by directly affecting liver function and causing metabolic disorders [15]. These chemicals can act alone or in combination as agents of obesity and diabetes [7]. Studies have shown that pesticide contamination can also affect metabolic syndrome. Acute and chronic exposure to chlorpyrifos has been found to cause weight gain, changes in lipid homeostasis, and increased blood pressure in exposed organisms [16], [17].

3. MODELING OF ENVIRONMENTAL POLLUTANTS EXPOSURE-INDUCED METABOLIC SYNDROME IN FISH

Model organisms have been preferred in scientific studies for many years. Among the fish species frequently used in aquatic pollution modeling, zebrafish embryos and larvae in particular have genes encoded for carbohydrate metabolism similar to those found in mammals [18]. Additionally, similar mechanisms are involved in lipid metabolism, pancreatic systems, and endocrine secretions. For this reason, it is preferred as a model organism, particularly in the study of diseases related to glucose metabolism [2]. In addition to the similarity of pancreatic structure, the similarity in normal blood glucose levels (human: 70–120 mg/dL; adult zebrafish: 50–75 mg/dL) has allowed the use of zebrafish models in which diabetes has been induced [19], [20]. These models aim to enable a more detailed assessment of obesity and diabetes risk in humans and to set new targets for treatment [21]. In terms of protein metabolism, approximately 70% of these genes have orthologs in humans. This facilitates their use in modeling cancer, cardiovascular disorders, metabolic disorders, and neurodevelopmental differences [22].

3.1. Diabetes

Diabetes mellitus is a condition defined as long-term high blood sugar levels. Physiologically, blood sugar levels are regulated by hormones. At the end of this complex process, sometimes these adjustments cannot be made, resulting in uncontrolled blood glucose levels. Zebra fish liver genes (atp5 and atp5gb3b) play a role in insulin resistance associated with obesity [2]. Due to the rapid recovery of β cells in zebrafish, cell damage is difficult to occur. Furthermore, if damaged, α cells can replace β cells [23].

Fish can also be used in research on retinopathy and nephropathy, which can occur as a result of diabetes. Organ damage, pathophysiology, and treatment strategies can be studied using model organisms [22], [24]. Significantly, recent data indicate that diabetes and obesity in fish have a detrimental effect on brain plasticity, cerebral oxidative stress, neuroinflammation, and neurogenesis [25].

3.2. Obesity

Obesity is a metabolic disorder that is becoming increasingly prevalent worldwide. Impaired lipid metabolism also leads to problems with energy balance. It is associated with polygenic induction and environmental effects [26]. It should be evaluated alongside other metabolic disorders due to leptin and insulin pathways. For example, it is thought that brain and hormonal activities contribute to metabolic disorders by affecting food intake [27]. Obesity also increases the risk of metabolic disorders such as hyperlipidemia, cardiovascular disease, diabetes, and cancer [2].

Exposing zebrafish larvae to obesogenic chemicals such as tributyltin has been observed to increase adipogenesis and obesity [28]. In another study, it was determined that exposure of zebrafish to bisphenol A (BPA) and tetrabromobisphenol A (TBBPA) affected food intake and caused obesity in zebrafish by activating the CB1 (cannabinoid receptor type 1) receptor [29]. Research conducted on zebrafish larvae exposed to bisphenol S showed that, compared to the control group, there was an increase in visceral fat accumulation, the genetic structure of lipid metabolism was affected, and as a result, obesity was caused [30]. Studies have shown that different persistent organic pollutants can have an effect on diabetes and other components associated with metabolic syndrome [10], [12], [13], [31].

3.3. Hypertension

Hypertension is a medical condition characterized by consistently high arterial blood pressure. The renin-angiotensin-aldosterone system (RAAS) is the hormone system that regulates blood pressure. Renin secreted by the kidneys causes angiotensin-converting enzyme (ACE) secreted by the lungs to convert angiotensin I (Ang I) to angiotensin II (Ang II). The increase in Ang II causes tubular epithelial cells to secrete more aldosterone, thereby promoting sodium reabsorption and potassium excretion in urine [32]. The gene for the renin enzyme is also found in zebrafish and shares approximately 50% homology with the gene for the renin enzyme in humans [33]. Although zebrafish continue to be used as a model for cardiovascular diseases, their relationship with metabolic syndrome has not yet been fully established. It is anticipated that advanced research will be conducted on hypertension resulting from chemical exposure, dietary changes, and genetic mutations [2], [34].

3.4. Dyslipidemia

Dyslipidemias are among the most common chronic diseases. It is characterized by abnormal serum cholesterol, triglyceride, or both elevated levels. The most common clinical findings include high levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides (TG), along with low levels of high-density lipoprotein (HDL), which are associated with cardiovascular disease risks [35]. In zebrafish, excess nutrients are stored in white fat cells in the form of lipid droplets, similar to mammals [36]. Adipocytes begin to appear approximately 7 days after the start of feeding (Figure 2), and have been observed in zebrafish larvae stained with nil red in studies, but no fat cells were observed in animals whose feeding was restricted [37].

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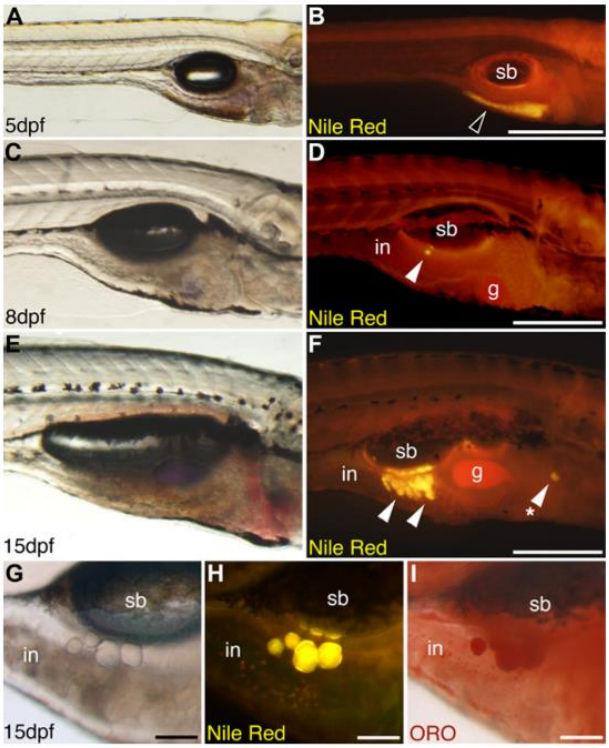

Figure 2. This figure, taken from Flynn et al. (2009), shows Nile Red staining in zebrafish at days 5, 8, and 15 post-fertilization. A, C, E, G (Bright field) and B, D, F, H (corresponding fluorescence images). Neutral lipid depots appear yellow. 15-day-old zebrafish stained with Nile Red (G, H) and then stained with ORO (I) show the localization of fat cell neutral lipid droplets. sb (Swim bladder), g (gall bladder), and in (intestine) are abbreviations used [8]

Fish also serve as an important model for the study of fat stores [38]. Additionally, the intestinal cholesterol absorption process is similar between zebrafish and humans [36], [39]. In a study conducted in 2011, the obesogenic effect of tributyltin was investigated using juvenile Oncorhynchus tshawytscha. Plasma triacylglycerol, cholesterol, and lipase levels showed increases at all doses administered, while glucose and insulin-like growth factor (IGF) levels showed increases only at low doses. The fact that chemical concentrations in the environment are generally low highlights the significance of the findings of this study [40]. In a study conducted in 2022 to determine the effects of environmental pollutants, zebrafish larvae were exposed to Bisphenol S (BPS) at concentrations of 0, 1, 10, and 100 µg/L for 15 days. It has been found that it triggers atherosclerotic cardiovascular disease, including an inflammatory response, macrophage recruitment around blood vessels, and oxidized LDL accumulation in the vascular endothelium. After 45 days of exposure to BPS, fatty acid metabolism is activated and peroxisome proliferator-activated receptor signaling is activated in the larval liver, leading to an increase in plasma LDL. Lipid accumulation, hyperlipidemia, erythrocyte aggregation, and increased levels of leukocytes and platelets in plasma were observed in the caudal artery of zebrafish larvae [41].

4. LIMITATIONS OF USING FISH AS A METABOLIC SYNDROME MODEL

Because the macro and micronutrient requirements of mammals, specifically humans, and fish differ significantly, it is quite difficult to correlate data obtained from studies conducted on fish with the human diet. Due to their poikilothermic nature, their development, metabolic rate, and body fat composition are

also affected by these characteristics. Furthermore, limitations arise in metabolic research because not all metabolic pathways have been studied in fish [42]. Lipid metabolism genes are not fully conserved in fish. For example, the leptin protein, an adipostatic hormone that regulates fat levels found in zebrafish, shows only 19% homology with the protein found in humans [21]. Another difference is that leptin and its receptor are not expressed in adipose tissue in zebrafish, but rather play a role in glucose homeostasis [43]. The different hepatic structure of fish, their lack of certain metabolic tissues and organs, their higher metabolic rate, and their shorter lifespan can lead to results that differ significantly from those of mammals, particularly in disease modeling and therapeutic responses [18], [22], [44]. All these differences should be taken into account when interpreting the results of fish modeling.

5. CONCLUSION

Metabolic syndrome is a critical disease characterized by multiple factors, the development of which can be induced by environmental pollutants as well as genetic predisposition. The relationship between chemicals such as endocrine disruptors, persistent organic pollutants, pesticides, and heavy metals and metabolic disorders has been supported by numerous studies. These studies have been explained in detail in previous sections. It is thought that exposure to these chemicals in a mixture can produce more potent and unpredictable effects than exposure to them alone. In this context, it is now an undeniable fact that environmental pollution directly affects not only ecosystem health but also human health.

In these research processes, the use of fish, particularly zebrafish, as model organisms offers a powerful research tool for understanding the effects of environmental toxins on metabolic health. The similarity between the genetic, physiological, and metabolic systems of zebrafish and humans makes this species suitable for metabolic disease modeling. Metabolic syndrome components such as obesity, diabetes, dyslipidemia, and potentially hypertension can be successfully studied in toxicological studies thanks to models developed using various chemicals on zebrafish. This situation provides an important basis for understanding the mechanisms of diseases and evaluating possible treatment approaches. Nevertheless, the poikilothermic nature of fish, their different feeding physiology, short life cycles, and the fact that some metabolic pathways do not fully correspond to those of mammals limit the direct generalization of the data obtained to humans. Therefore, while carefully evaluating the advantages offered by fish models such as zebrafish, it is also important to consider their limitations In order to better understand the effects of environmental toxins in the future, data obtained from fish models must be subjected to comparative analysis with mammalian models and human cell cultures, and a multifaceted approach must be adopted. This will enable the development of more effective strategies for the prevention and management of complex diseases such as metabolic syndrome.

As a result of our study, recommendations for future research can be listed as follows:

Long-term exposure models: Chronic and multigenerational studies in fish should be emphasized to assess cumulative and transgenerational impacts of pollutants.

Therapeutic strategies: Zebrafish models can be utilized to explore preventive and therapeutic interventions for metabolic syndrome components.

Integrated methodology: Application of multi-omics (genomics, transcriptomics, metabolomics) approaches will provide a more comprehensive understanding of pollutant-induced metabolic disruptions.

Comparative approaches: Systematic comparison of fish model data with mammalian models and human cell cultures is essential to improve translational relevance.

Mixture toxicity studies: Research should prioritize the combined effects of multiple environmental pollutants, as mixtures may induce more potent and unpredictable outcomes.

Molecular mechanisms: Detailed investigations into conserved and divergent metabolic pathways between fish and humans will help clarify mechanistic connections.

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The Declaration of Conflict of Interest/ Common Interest

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Author's Contribution

The author contributed 100% to the study.

The Declaration of Ethics Committee Approval

This study does not require ethics committee permission or any special permission.

Declaration of research and publication ethics

The authors of the paper declare that we followed the scientific, ethical and citation rules of Environmental Toxicology and Ecology in all processes of the paper and that we did not make any falsification of the data collected. Furthermore, we declare that ETOXEC and its Editorial Board are not responsible for any ethical violations that may have occurred and that this study has not been evaluated in any other academic publication environment than ETOXEC.

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