Concept Paper

Lifetime Exposure Model of Type 2 Diabetes

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Lifetime Exposure Model of Type 2 Diabetes

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ABSTRACT: Type II diabetes (T2D) is a multifaceted metabolic disease influenced by various factors (genetic, epigenetic, environmental, and other). An alarming surge in T2D prevalence is estimated, reaching 700 million cases by 2045 worldwide. This review explores the complex interactions of multiple risk factors throughout life and offers a new perspective on T2D. Genetic and epigenetic influences are described in detail. Prenatal factors, such as exposure to undernutrition and maternal overfeeding, induce lasting epigenetic changes, affecting T2D susceptibility. Furthermore, birthweight is a crude proxy for perinatal programming, with low and high birthweights associated with increased T2D risk. Often overlooked, the early postnatal period also significantly contributes to perinatal programming. Neonatal over-nutrition and feeding choices exert lasting effects on DNA methylation and metabolic outcomes later in life. Stress during this period further exacerbates T2D susceptibility. In continuation, childhood behaviors which are influenced by prior periods contribute substantially to T2D risk. Adverse childhood experiences amplify the risk of many diseases, including T2D. Sleep hygiene throughout life plays a role in metabolic health, influencing insulin resistance and appetite regulation. In adulthood, obesity remains a prominent predictor of T2D, with chronic stress contributing to weight gain and unhealthy lifestyle. This review proposes a novel perspective, considering T2D pathophysiology as a nonlinear process governed by numerous factors and their interactions throughout life. The inherent unpredictability suggests a need for personalized interventions tailored to specific risk profiles, emphasizing the importance of understanding gene-environment interactions and embracing a holistic view of T2D pathogenesis.

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INTRODUCTION

Type II diabetes (T2D) is a complex multifactorial disease with both genetic and environmental components. According to estimates, in 2019 more than 460 million adults worldwide suffered from T2D, though about half were undiagnosed [1]. Based on its dramatic increase in prevalence, it is projected that by 2045 approximately 700 million people will live with this disease [1]. T2D is burdensome for patients, as it decreases quality of life and life expectancy, but also for the society at large with immense costs on health systems. Progression of this disease usually takes years [2], as patients first go through prediabetic state, which precedes full-blown T2D. Prediabetes is defined by at least one of the following metabolic conditions: elevated fasting glucose levels, impaired glucose tolerance or increased glycated hemoglobin A1c (HbA1c) levels [3].

Plethora of risk factors for T2D have been identified: obesity, sedentary lifestyle, chronic stress, insufficient sleep, smoking, excessive fructose intake, family history, ethnicity, and others [4–8]. Even though some of those factors are more prevalent than others, individuals generally present with diverse sets of risk factors – one 'group' of patients might have completely different set of risk factors compared to another. Consequently, those provisional 'groups' of patients might benefit more from distinct sets of interventions. Early pharmacological intervention can in some cases prevent progression of prediabetes to T2D [9]. Bariatric surgery, low-calorie diets, and carbohydrate-restricted diets all proved as useful therapeutic interventions, reversing T2D in short-term with varying success rates [10]. Despite promising results, none of these displayed consistent success, and long-term outcomes were worse compared to short-term. In this review, I present a theoretical model that tries to reconcile pathogenesis of T2D and so far, unsuccessful attempts of T2D reversal –

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speculating that these processes are governed by nonlinear dynamics; and as such are particularly sensitive to initial conditions.

GENETICS, EPIGENETICS AND PRENATAL ENVIRONMENT

At the time of conception, biological sex is determined by sex chromosomes. This single event has major implications for lifestyle choices and disease vulnerabilities later in life. Accumulating evidence shows tangible sex-specific differences in prevalence, pathophysiology, and outcomes of many chronic diseases, including T2D [11]. American Diabetes Association in their diabetes guidelines appreciates biological differences between males and females [12]. It should be noted that vast majority of genetic, epigenetic, and lifestyle factors discussed later in this paper act sex-specifically [11,13]. Moreover, sex hormones in male and female individuals differentially impact energy balance, fat accumulation, nutrient partitioning, inflammation, and other aspects of metabolism [14,15]. It seems that these sex differences render females more prone to T2D earlier in life, but males later in life [16]. However, this is a reductionist approach to T2D and when evaluating risk many other variables should be taken into consideration.

Major progress has been made in identifying genetic loci associated with increased risk of developing T2D, as reviewed by Brown and Walker [17]. Genome-wide association studies (GWAS) have been instrumental in this process – approximately 88 loci have been associated with T2D [18]. Significantly, majority of those loci are relevant to functions of pancreatic β-cells, and much less to insulin resistance (IR) *per se* [18]. Regarding GWAS results, it should be appreciated that many loci are population-specific [19–21]. Additionally, both parental origin of a given locus and sex of an individual influence the extent of association [22,23]. Therefore, it is conceivable that some populations disproportionately accumulate risk alleles correlated with β-cell function, while others might accumulate more alleles relevant to insulin sensitivity in peripheral tissues, e.g. skeletal muscle, liver etc., as has already been observed [24]. Future genomic studies could provide valuable insights into many of these nuances.

Despite substantial advances in identifying risk alleles for T2D, those recognized loci do not explain much of the observed T2D heritability [25], suggesting environmental and lifestyle factors which might affect epigenome. Individuals exposed to prenatal famine during Dutch hunger winter exhibited lasting changes in DNA methylation patterns. These epigenetic alterations were sex- and gestational timing-dependent and might have mediated chronic disease susceptibility later in life [26]. Similarly, prenatal maternal overfeeding alters epigenome in several ways that might make one predisposed to metabolic diseases, e.g. by altering hypothalamic insulin receptor expression [27]. Consequently, prenatal maternal feeding habits also influence neonatal birthweight [28]. Meta-analysis conducted by Harder et al. determined that both low and high birthweight were associated with increased risk of T2D later in life [29] though there are many other factors besides maternal nutrition that affect birthweight [30], and in this context, future risk of T2D.

Birthweight is a rather crude proxy of many underlying mechanisms [31]. Since 1970s, when Dörner first coined the term perinatal programming [32], major progress has been made in understanding perinatal effects of environment and hormones on subsequent disease predisposition [33]. Interestingly, most of the established risk factors for T2D in adult life are also relevant in perinatal programming, resulting in increased T2D risk in offspring – including, but not limited to: eating habits [28], obesity [34], chronic stress [35,36], sleep restriction [37] etc. Some of these are, in fact, sex- and gestational timing-dependent. Admittedly, there are many other relevant mechanisms affected by perinatal programming, including pancreatic β-cells' function and growth, gut microbiota, immune system regulation etc. [38]. However, defining all relevant aspects of perinatal programming is outside of the scope of this article, and isn't crucial for understanding, later proposed, underlying principle. Taken together, these findings suggest that an individual is more or less susceptible to development of T2D and possibly other metabolic diseases, based on one's genetic and epigenetic makeup, as well as prenatal environment. All of these factors should be viewed in terms of foundation upon which later-life risk factors build towards metabolic disease.

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EARLY POSTNATAL PERIOD

Evidently, there are some issues with studies examining perinatal programming by focusing exclusively on prenatal period, thoroughly reviewed by Plagemann et al [39]. As emphasized in that review, in the context of perinatal programming, neonatal environment has a considerable additional, if not even independent, effect on health in adulthood. Similarly, to epigenetic effects of prenatal maternal overfeeding, neonatal over-nutrition also leads to alterations of hypothalamic DNA methylation patterns within promoter region of insulin receptor [40]. Moreover, it has been demonstrated that early postnatal over-nutrition alters epigenome by modifying DNA methylation within promoter regions of genes critical for weight and appetite regulation in hypothalamus [41]. An elegant experiment in rodent model presented important caveat to apparent association of low birthweight and increased risk of metabolic disease in adults – low birthweight was associated with increased risk of metabolic dysfunction only when coupled with neonatal over-nutrition [42]. This caveat seems to be corroborated by epidemiological and clinical findings [39]. All of these data accentuate the importance of proper neonatal nourishment tailored to an individuals' needs.

When considering neonatal feeding, there are two main options, namely breastfeeding (BF) and formula-feeding (FF). BF is the preferred modality, and short-term effects, including reduced morbidity are well defined [43,44], while long-term benefits are still being elucidated. Interestingly, there is a dose-response association between BF duration and later risk of overweight – every month infant was breastfed (up to 9 months) was associated with 4% risk reduction of overweight as adult [45]. According to systematic-review and meta-analysis from 2015, it appears that BF is protective of T2D [46]. Furthermore, breastfed infants compared to formula-fed displayed slightly lower serum insulin as children and adults, admittedly this result was more consistent and pronounced in infancy [47]. These studies were mostly conducted with metabolically healthy mothers. Therefore, it is relevant to consider lactation of mothers with T2D. Even in these cases, BF is advised but proper glucose control should be maintained during lactation [48]. Importantly, diabetic mothers might produce breast milk of altered composition, with increased glucose and insulin concentrations [49,50]. In contrast, mothers with tightly controlled insulin-dependent diabetes produced milk of normal macronutrient content [50]. It should also be emphasized that maternal nutrition during lactation impacts breast milk composition [51]. Studies suggest that besides glucose, even hormones from breast milk can be absorbed by infant [52]. In particular, orally delivered leptin during suckling period improved insulin sensitivity, metabolic response of adipose tissue, and affected food preferences later in life [53–55]. Epigenetic effects of adequate leptin absorption from breast milk are well characterized, mainly on hypothalamic factors regulating food intake – these effects seem to be long-lasting [56]. On the other hand, infant formulas are often devoid of many biologically active substances, including leptin [57], which might explain worse health outcomes of formula-fed infants. Further research of breast milk composition, bioactive factors including hormones, growth factors, cytokines, adipokines and others, should provide valuable insights into perinatal programming during suckling period [58]. Nutrigenomics of BF could illuminate genes and breast milk-constituents' interactions which might render one prone to metabolic disease or, in contrast, provide protection [59]. In addition, these studies might also improve production of infant formulas in cases where BF isn't feasible.

Another important aspect that should be discussed in this period is postnatal stress. Hypothalamic-pituitary-adrenal (HPA) axis is a central mediator of stress response [60]. One example of a postnatal stressor would be extended hospitalization in neonatal intensive care units (NICU), and in some cases prolonged isolation from mother. Infants are especially sensitive of stressors. Stress in this period has many biological consequences in adulthood, of relevance to T2D pathogenesis are reduced insulin sensitivity [61], defective insulin secretion following psychological stressors [62], reduced β-cell quantity [63], higher levels of inflammatory markers (CRP and IL-6) [64], and many others [65]. Crucially, stress in this vulnerable period remodels HPA axis itself, resulting in reduced circadian variability of cortisol secretion and hypo- or hyper-responsive HPA axis to stressors later in life [65–67]. This is of particular interest for adults exposed to chronic stress.

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Based on studies presented in prior paragraphs, it is becoming clear how an individual could at this early period, already have significantly increased risk of developing T2D in adulthood. For example, if maternal nutrition was insufficient during pregnancy, there would be an increased risk of infant low birthweight. Infant with low birthweight would therefore have increased risk of admission to NICU [68], where he/she would likely be isolated from mother and formula-fed. If infant was indeed formula-fed, there would then be increased risk of rapid weight gain (as compared to breastfed infants) [69]. As previously mentioned, low birthweight coupled with rapid postnatal weight gain would exacerbate preexisting tendencies for metabolic disorders [42]. Moreover, prolonged hospitalization in NICU would be a major stressor for infant and would impact many aspects of glucose homeostasis and stress response. These negative effects could, in theory, nonlinearly 'add up' and render individual more vulnerable to many other risk factors later in life and ultimately lead to T2D.

CHILDHOOD AND ADOLESCENCE

Even though early postnatal period is crucial in terms of perinatal programming of metabolic diseases in adulthood, not everyone who develops T2D encountered some of the aforementioned adversities, and vice versa. Indeed, behaviors in childhood have many implications for health later in life. One of the major concerns in this area of research is childhood overweight and obesity. Dramatic increase of childhood obesity in period from 1975 to 2016 has been observed: in 1975 there were 5 million obese girls and 6 million boys, whereas in 2016 these numbers have risen to 50 and 74 million, respectively [70]. Above-average childhood body mass index (BMI) values during ages 7 to 13 are associated with increased risk of developing T2D [71]. Significantly, these above-average BMI values were lower than conventional definitions of overweight. Additionally, this association was present even when adjusted for birthweight; it was stronger in younger birth cohorts, and in females compared to males. Another study of Danish men elucidated modifiable aspect and window-of-opportunity for childhood overweight. To be more specific, overweight boys that reduced BMI (and maintained thus reduced values) between 7 and 13 years of age had similar risk of T2D diagnosis at 30 to 60 years of age as men who had never been overweight [72]. On the other hand, being overweight during puberty and early adulthood was associated with greater risk of T2D than being overweight in earlier periods. This particular study pinpointed childhood period before puberty as an important opportunity for intervention in overweight children.

Another aspect of childhood that should be considered is exposure to adverse childhood experiences (ACEs). ACEs is a unifying term for traumatic events that take place during childhood, e.g. exposure to abuse, neglect, violence, family instability, substance abuse and others [73]. Despite difficulties at estimating global ACEs prevalence, some patterns do emerge that define more vulnerable groups – females are at increased risk of ACEs, as well as ethnic minorities [74,75]. Exposure to ACEs has so far been linked to many morbidities in adulthood, including T2D [76,77]. Deleterious consequences of ACEs on health are explained through Biological Embedding Model [78]. According to this model, early stress is programmed into macrophages, which then exhibit proinflammatory phenotype. This is characterized by excessive cytokine reaction to challenge and decreased response to anti-inflammatory signals. Over a lifetime, inflammatory state is further exacerbated by unhealthy behaviors and hormonal dysfunction, resulting in inflammation-driven pathogenesis of many chronic diseases. Furthermore, exposure to ACEs increases HPA axis activity and tendencies towards unhealthy behaviors later in life, i.e. poor diet, sedentary behavior, heavy alcohol use etc. [79–81]. Interestingly, chronic low-grade inflammation, mediated by infiltration of proinflammatory macrophages in tissues central to insulin action, is described in pathogenesis of T2D [82]. Indeed, it is plausible that exposure to ACEs plays a significant contributing role in some diabetic patients.

On average, about a third of human life is spent sleeping [83]. Maintaining proper sleep hygiene is important for glucose homeostasis [84], and overall metabolic health [85]. Sleep duration of children and adolescents has rapidly declined in modern times [86]. It is advised that adolescents get between 8 to 10 hours of sleep per day [87], though data suggest that between one fifth and one third

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of adolescents suffer from some form of sleep disorder [88]. Concerning rise of sleep disorders in this age group is probably linked to increased screen time and internet usage before bed [89]. Insufficient sleep is associated with many unfavorable health outcomes – it is a significant factor to both childhood obesity and T2D [90,91]. Observational studies in children and adolescents indicate association of decreased sleep quantity and quality with insulin resistance, however experimental research is inconsistent and sparse [91]. On the other hand, studies examining sleep restriction and weight gain are consistent: sleep restriction increases food intake, hunger, and appetite [92–94]. Therefore, chronic sleep restriction most likely can promote weight gain in children and adolescents, and thereby increase subsequent risk of T2D.

ADULTHOOD

At this point, it is evident that genetic and epigenetic makeup, alongside environmental influences at life stages before adulthood, can significantly increase susceptibility to T2D. Moreover, these same factors can also influence lifestyle choices, increasing tendencies towards unhealthy behaviors. Majority of risk factors for T2D and their role in T2D pathogenesis are characterized in adults but prior influences should still be kept in mind.

In adults, obesity or overweight by itself appears to have the most predictive value of T2D [95]. Similar to prior life stages, time-period of weight gain seems to matter even in adulthood – bodyweight increase in early adulthood (between ages 25 and 40) was associated with increased risk and earlier onset of T2D compared to weight gain in later period (between ages 40 and 55) [96]. Extending from results of previously mentioned study [72], it seems that being overweight or obese in period spanning from puberty till the end of early adulthood (approximately through ages 13 to 40) significantly increases T2D risk and probability of an earlier onset. These findings could be leveraged in terms of societal interventions in children before puberty, e.g. by encouraging physical activity in school or extracurricularly, by learning to pick healthier food choices etc. Population-specific phenomena regarding BMI should also be considered. Compared to Caucasians, Asians usually have higher proportion of adipose tissue or degree of visceral adiposity for the same BMI value [97–99]. Therefore, some conventional obesity markers, like BMI might not be suitable for all populations and more sophisticated and population-specific measures should be obtained [98].

Chronic stress is recognized as a major contributor to weight gain [100]. Chemicals released during stress response are generally considered hyperglycemic, they increase insulin secretion and hepatic gluconeogenesis, alongside other effects [101,102]. Metabolic and other problems arise when the state of stress becomes chronic [103]. Individuals with history of ACEs can exhibit hyperactive HPA axis and are more likely to suffer from prolonged stress [81]. Chronic stress has both direct and indirect impact on glucose homeostasis. Direct effects are mediated by previously mentioned stress response chemicals which ultimately decrease insulin sensitivity [104,105]. Indirect effects, on the other hand, are mainly reflected in unhealthier lifestyle choices, e.g. poor diet, sedentary lifestyle [106]. Chronic stress increases intake of food with higher carbohydrate and saturated fat content, as well as total caloric intake [107]. These diet alterations can directly promote obesity. Studies examining diet-type and T2D risk are vastly inconsistent and at this point there is no conclusive evidence [108]. If not directly, diet modification elicited by chronic stress might increase risk of T2D at least by indirect means, through increased risk of obesity. Other indirect effects are also plausible – chronic stress is associated with poor sleep hygiene [109], decreased physical activity [110,111], dysregulated inflammatory pathways [112] etc. It should be noted that many of these associations don't specifically imply causation. It is likely that most of these interactions are bidirectional – chronic stress does promote worse sleep, but poor sleep also promotes chronic stress.

TYPE 2 DIABETES AS CHAOTIC PROCESS

Nonlinear dynamical systems, in contrast to linear systems, are characterized by output variations that are not proportional to input variations [113]. These systems are inherently chaotic and are often described as unpredictable. Herein we propose that T2D could be viewed as chaotic process, governed by numerous factors and their interactions throughout lifetime (Figure 1). Some of

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these factors are well defined and identified as risk factors for T2D, presumably many more are yet to be described. Many of known risk factors are omitted from this paper for the sake of simplicity – this does not in any way mean that they are considered of minor importance. Continuing from this perspective, individuals might end up with T2D mediated by different sets of risk factors, and consequently slightly different pathophysiology. It is plausible that there are pathophysiologically dissimilar phenomena leading towards dysregulated glucose homeostasis and described by the common term T2D. This is in agreement with the findings that risk scores for T2D usually have good predictive value only in populations from which they were developed, but not in external populations [114]. Although thus proposed inherent unpredictability might be considered as a major limitation of this model, it is not necessarily so. Stratifying populations based on individual risk assessment could elucidate which cohorts would have greater benefits of specific preventive actions. By identifying more sensitive life periods to these risk factors and addressing them appropriately – similar to identifying period before puberty as especially important in weight reduction in overweight children – it would be easier to tailor suitable interventions at societal and individual levels that would have a major influence on final output, i.e. development of T2D in individuals.

Furthermore, not only that interactions of (risk) factors in pathogenesis are still rarely considered in human subjects but in experimental models as well. Part of this problem is starting to be addressed by developing areas of research. One example of this is nutrigenomics – main theme of this research area is discovering nutrient-genome interactions and how those could drive disease [115]. Other gene-environment interactions are also gaining research interest, including gene polymorphisms interaction with smoking and physical activity on risk of T2D [116]. In theory, some interactions and their consequences seem to be well established. Individuals exposed to chronic stress are more likely to suffer from decreased sleep quality [117], which might influence their food choices, and predispose them towards obesity [118], and thus increase their risk of developing T2D. This particular instance seems to have apparent cause-effect components and is often referred to as a 'vicious-cycle'. However, these 'vicious-cycles' are rarely experimentally scrutinized even in laboratory models, and when examined in detail they exhibit important interactions between their core components. In order to get a clear understanding of these interactions at molecular, neuroendocrine, and other levels, it would be beneficial to emulate these states as close as possible in laboratory models, despite many technical difficulties. Patients with T2D most often do have more than one risk factor. Thus, to get most out of treatment, understanding interactions is of great value. This holistic view of T2D being the ultimate 'output' of dynamical system, i.e. life through prenatal period all the way to the present life stage, could benefit patients and might offer adjunct patient-tailored interventions, alongside currently available practices.

DECLARATION OF COMPETING INTEREST

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No funds were received in support of this study.

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