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REVIEWS

Role of vitamin D in modulating gestational diabetes

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Low maternal levels of major circulating form of vitamin D could be a perplexing factor that leads to expression of gestational diabetes mellitus (GDM). Insufficient or deficient levels of vitamin D may allow diabetic insult during pregnancy leading to gestational diabetes and inducing changes in a variety of key functional molecules and gene expression. Autocrine metabolism of vitamin D promotes anti-inflammatory response to maternal decidua and fetal trophoblasts. Immunomodulatory actions of vitamin D are likely to be compromised under conditions of low vitamin D levels with potential detrimental physiological consequences. Recent data are now available to implicate autocrine/paracrine impact of maternal vitamin D status can result in both increased insulin resistance and reduced insulin secretion, linking inflammation to metabolic disorder in the mother. Insulin and cytokines are the main contributors to the cascade of events and potential regulators of placental function in GDM. This article aims at exploring the possible mechanisms underlying GDM that could be regulated by pleotropic effects of vitamin D.

Keywords. vitamin D, gestational diabetes, placenta, insulin, immune response.

Introduction. Exposure of skin to sunlight results in the endogenous synthesis of vitamin D and hydroxylation to its active form under the influence of ultraviolet B (UVB) radiations (wavelength 290–320 nm) [1]. Vitamin D is then transported to the liver and converted to 25-hydroxy-vitamin D (25(OH)D). There is no significant storage of 25(OH)D in the liver and is rapidly released into the blood for a biological half-life of approximately 12–19 days. In the skin, a plateau of daily vitamin D production is reached after only 30 min of UVB rays [2]. Increased melanin pigmentation of skin reduces the efficiency of UVB-mediated vitamin D synthesis and necessitates the increase in exposure time required to maximize vitamin D formation, but does not influence the total content of daily vitamin D production.

In kidneys, 25(OH)D is enzymically converted to the active vitamin D hormone 1,25-dihydroxyvitamin D (calcitriol). Renal synthesis of calcitriol is homeostatically controlled by parathyroid hormone (PTH) [2, 3].

Within the last two decades, the vitamin D receptor (VDR) has been shown to be present not only in classical target tissues such as bone, kidney, and intestine, but also in many other nonclassical tissues, for example, in the immune system (T and B cells, macrophages, and monocytes), in the reproductive system (uterus, testis, ovary, prostate, placenta, and mammary glands), in the endocrine system (pancreas, pituitary, thyroid, and adrenal cortex), in muscles (skeletal, smooth, and heart muscles), and in brain, skin, and liver. Besides the presence of VDR, different cell types (for example, keratinocytes, monocytes, bone, placenta) are capable of metabolizing 25-hydroxyvitamin D to $1,25(OH)_2D$

by the enzyme 25(OH)D-1α-hydroxylase, encoded by the gene *CYP27B1*. The combined presence of *CYP27B1* and the specific receptor in several tissues introduced the idea of a paracrine/autocrine role for $1,25(OH)_2D$ [1]. It is quite feasible for a low vitamin D status to increase the risk of a wide range of disease states. A 25(OH)D level of 75 nmol per 1 l (30 ng per 1 ml) or higher provides adequate substrate for 1-α-hydroxylase to convert 25(OH)D to its active form, $1,25(OH)_2D$ (1,25-dihydroxyvitamin D) [4].

Serum concentrations of $25D_3$ below 75 nM are now considered to be inadequate and are more commonly referred to as vitamin D «insufficiency» as opposed to «deficiency». We categorized the serum levels of 25-hydroxyvitamin D [25(OH)D] as: less than 38 nM (20 ng per 1 ml) as deficient, 38–80 nM (20–30 ng per milliliter) as insufficient, and 80–150 nM (30–60 ng per 1 ml) as sufficient [5].

During pregnancy, vitamin D is important for helping beta cells of the pancreas to keep up with growing insulin demand. It helps the parathyroid glands make calcitonin, the hormone that moves calcium into the tissues where it needs to go. Calcitonin triggers the release of insulin from the beta cell «pockets» in which is it stored in the pancreas, keeping up with the greater demand for insulin by mother and developing child [5].

Gestational diabetes. Gestational diabetes mellitus (GDM) or high blood sugar (hyperglycemia) that starts or is first diagnosed during pregnancy is also known as glucose intolerance during pregnancy. It can cause the body to be less sensitive to the effect of insulin. These changes can lead to high blood sugar and diabetes. High blood sugar levels in pregnancy are dangerous for both mother and fetus. Hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes mellitus. The mechanisms underlying this phenomenon are likely to be multifactorial [6]. Wolf et. al. [7] suggested that inflammation is associated with the development of GDM and may be another pathophysiological link between GDM and the onset of future type 2 diabetes.

Placental inflammation and insulin receptors play a prominant role in the onset of GDM which could both be regulated by vitamin D.

Placental development in gestational diabetes. The placenta is a complex organ playing pleiotropic roles during fetal growth. It separates the maternal and fetal compartments, with which it is in contact through different surfaces. The syncytiotrophoblast exposes the placenta to the maternal circulation whereas the endothelium is in contact with fetal circulation. Because of this unique position, the placenta is exposed to the regulation by hormones, cytokines, growth factors, and substrates present in both circulations and therefore, affected by either of them. At the same time, it can produce molecules that will affect mother and fetus independently [8].

Placental development involves three distinct phases. At the beginning of gestation, a series of critical proliferation and differentiation processes (predominantly of the trophoblast) lead to the formation of new villi and extravillous structures. These structures anchor the placenta in the uterus and remodel the uterine spiral arteries into low resistance vessels. The newly formed villi mature through various steps of differentiation. The end of gestation is associated with placental mass expansion involving villous growth (Fig. 1). During the first half of gestation in placenta, the trophoblast is the key tissue that undergoes the most profound alterations, whereas extensive angiogenesis and neovascularization occur in the second half of gestation, i. e., the endothelium is the site of the more prominent processes, although there is overlap [9].

Onset of diabetic alterations at the beginning of gestation (as in many pregestational diabetic pregnancies) may have long-term effects on placental development. These adaptive responses of the placenta to the diabetic environment, such as buffering excess maternal glucose or increased vascular resistance, may limit fetal growth within a normal range. If the duration or extent of the diabetic changes, including maternal hyperglycemia, hyperinsulinemia, or dyslipidemia, exceeds the placental capacity to mount adequate responses, then it may lead to excessive fetal growth and macrosomia.

Diabetic condition at later stages in gestation, such as may occur in gestational diabetes, would lead to short-term changes in a variety of key functional molecules and the gene expression [10].

Immune response in gestational diabetes. In a recent study, GDM was linked to the down-regulation of Th1 (pro-inflammatory T-helper cells) cytokines along

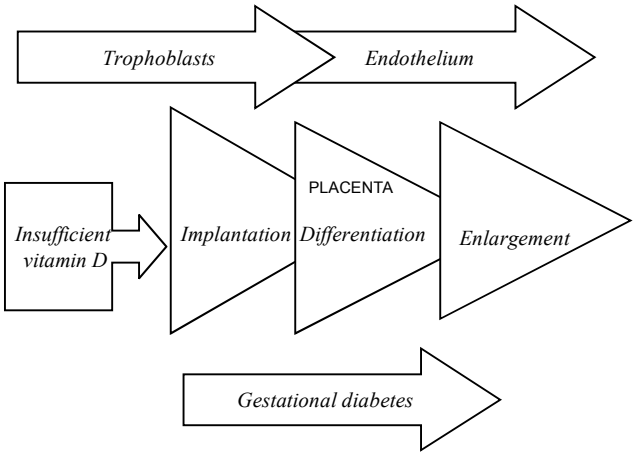

Fig. 1. Development of placenta. Placental development occurs in three distinct, yet overlapping phases. First half of gestation is predominantly associated with the trophoblast and the second half of gestation with the endothelium. Vitamin D insufficiency or deficiency could make it susceptible to develop diabetes changes at later stages in gestation such as in GDM with short-term effects predominantly on placental function rather than its structure

with adiponectin and up-regulation of inflammatory cytokines and leptin. Serum adiponectin levels were decreased, whereas the concentrations of leptin, inflammatory cytokines, such as IL-6 and TNF-α, were significantly increased in gestational diabetic mothers compared with control women. Serum concentrations of T-helper type 1 (Th1) cytokines (IL-2 and interferon-γ) were decreased, whereas IL-10 levels were significantly enhanced in gestational diabetic mothers compared with control women [11].

It has been well propounded that during normal pregnancy, Th1 cytokines are down-regulated, whereas cytokines belonging to Th2 cells (anti-inflammatory T-helper cells) are up-regulated [12]. Besides, a shift of Th1 phenotype to Th2 during pregnancy has been shown to encourage vigorous production of antibodies that not only combat infections during pregnancy but also offer passive immunity to the fetus [13]. In this study it was shown that serum IL-2 and IFN-γ concentrations are down-regulated, whereas IL-4 concentrations were not altered in gestational diabetic mothers. Interestingly, the levels of IL-10, a Th2 cytokine, were elevated in these diabetic mothers. These suggest that diminished concentrations of Th1 cytokines and increased IL-10 levels may be implicated in maintaining the pregnancy in gestational diabetic women.

The placenta (in addition to cells of immune system and the adipose tissue) also synthesizes a variety of cytokines, tiering an additional level of complexity to the immune-metabolic network existing in pregnant individuals. This raises the possibility that placenta cytokine production contributes to a low-grade inflammation developing during the third trimester of pregnancy [14]. In pregnancy complicated with GDM or obesity, there is a further dysregulation of metabolic, vascular, and inflammatory pathways supported by increased circulating concentration of inflammatory molecules [15, 16]. Studies of transcriptional profiling have shown that adipose tissue and the placenta express a common repertoire of cytokines and inflammation-related genes, which become over expressed in a diabetic environment [17, 18]. The current view is that placenta in addition to the adipose tissue, contributes to the inflammatory situation by releasing inflammatory molecules.

Insulin receptors in placenta. The placenta expresses high amounts of insulin receptors relative to other tissues in the body. Their location undergoes developmental changes. At the beginning of gestation, they are located at the microvillous membrane of the syncytiotrophoblast, whereas at term, they are predominantly found at the endothelium [19, 20] (Fig. 2). The evidence suggests a shift in control of insulin-dependent processes from the mother at the beginning of pregnancy to the fetus at the end. The change in insulin receptor location is paralleled by a change in function, since insulin-induced gene expression is highest in first trimester trophoblast [21]. At term, insulin has a stronger effect on the endothelium than on the trophoblast. This is important for diabetic pregnancies in general and for GDM in particular, because it can be assumed that the fetal hyperinsulinemia will affect the placental endothelium.

Fetal insulin in normal pregnancies and even more so in diabetic pregnancies with hyperinsulinemia may alter the expression of genes [21], or stimulate endothelial glycogen synthesis [22]. Enhanced glycogenin (the protein precursor for glycogen synthesis) gene expression in placenta with GDM has also been reported [10]. It is possible at the beginning of pregnancy, maternal insulin regulates the placenta by interacting with the syncytiotrophoblast. This may lead to altered synthesis and secretion of hormones and cytokines that in turn

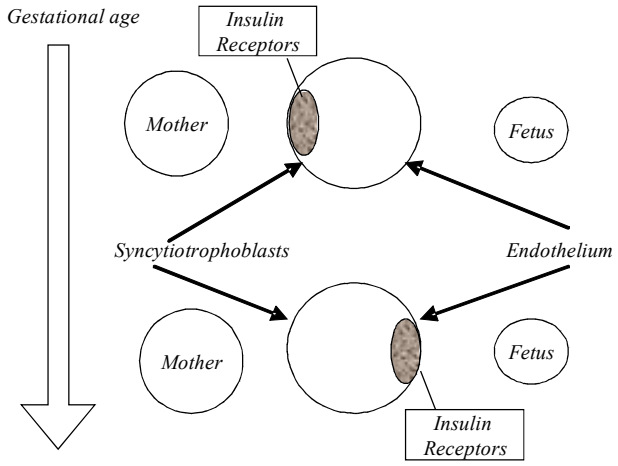

Fig. 2. Shift in insulin receptors in placenta with gestational age. Microvilli expose placenta to the maternal side whereas the endothelium is in contact with fetal circulation. At the beginning of gestation, the insulin receptors are located at the microvillous membrane of the syncytiotrophoblasts , whereas at term, they are predominantly found at the endothelium, suggesting a shift in control of insulin-dependent processes from the mother at the beginning of pregnancy to the fetus at the end

will act back on the mother, thus forming a feedback loop. As gestation advances, the fetus, i. e., fetal insulin, will gradually take over control from the mother and directly or indirectly affect the endothelium or tissue-resident macrophages [21].

Role of placenta in gestational diabetes. In addition to immune related cytokines and growth factors, the placenta synthesizes two adipokines: resistin and leptin (adipose tissue-specific proteins) implicated in the regulation of insulin action [23]. The discovery that some of these adipokines are key players in the regulation of insulin action suggests possible novel interactions between the placenta and adipose tissue in understanding pregnancy-induced insulin resistance. The interplay between the two systems becomes more evident in GDM [10]. Different types of placental cells produce different cytokines: the Hofbauer cells produce TNF-α [24, 25], the syncytiotrophoblast is the major site of leptin synthesis, trophoblast cells and vascular endothelium produce IL-6 [26, 27]. Studies of the pattern of production and release of placental cytokines into the systemic circulation have provided valuable information relating to their mechanism and site of action. Leptin and IL-6 are released into the fetal and maternal systemic circulation. Thus, they can exert endocrine action by acting at sites remote from the production site [28, 29]. In contrast to leptin, TNF-α is poorly released from the placenta and hence is more likely to exert local paracrine effects. There is an overproduction of placental leptin and TNF-α in type 1 diabetes and GDM [30]. In GDM, the overexpression of placenta TNF-α is associated with increased fetal adiposity [10].

TNF-α may also participate in the endocrine mechanism of pregnancy-induced insulin resistance by adding a placental component to the insulin resistance developing in the mother [29].

Hence, the abnormal maternal metabolic environment (hormones, nutrients, cytokines) may generate stimuli within the adipose tissue and the placental cells resulting in the increased production of inflammatory cytokines. These events link inflammation to metabolic changes by enhancing insulin resistance in the mother. Similar changes occur in the fetal environment in diabetes, and elevated levels of insulin, leptin, and other cytokines have been well documented (Fig. 3). Insulin and cytokines are the main contributors to the cascade of events and potential regulators of placental function in GDM.

Vitamin D and regulation of insulin levels. The dependence of normal insulin secretion in pancreatic beta-cells on vitamin D has been for decades. Experimental studies have demonstrated that a reduction in vitamin D activity can result in both increased insulin resistance and reduced insulin secretion [31]. Epidemiological data have shown a four- to five-fold higher prevalence of non-insulin-dependent diabetes in dark-skinned Asian immigrants in comparison with British Caucasians indicating that low vitamin D status may contribute to the pathogenesis of diabetes [32]. In elderly population the subgroup with the lowest range of 25(OH)D levels had a significantly higher blood glucose increase and higher blood insulin increase after an oral glucose-tolerance test in comparison with the subgroup with the highest range of 25(OH)D levels [33]. Data indicate that vitamin D insufficiency may result in insulin resistance.

Results are in line with the suggestion that enhanced levels of TNF-α, a cytokine with is inversely related to 25(OH)D and calcitriol promote insulin resistance [34].

A severe vitamin D deficiency probably results in low serum insulin levels indicating reduced insulin sec-

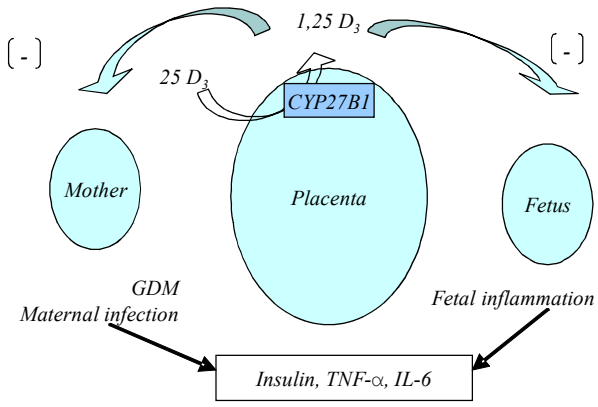

Fig. 3. Regulation of GDM by vitamin D. Placenta is capable of converting 25 D_3 to the active form 1,25 D_3 due to the abundance of CYP27B1. Vitamin D regulates the maternal infection, both local and systemic as well as fetal inflammation. Insufficient levels result in elevated levels of insulin, leptin and cytokines mainly TNF-α and IL-6. These events skew the metabolic changes towards GDM by enhancing insulin resistance in the mother

retion [31]. In uraemic patients, administration of vitamin D was able to improve blood glucose levels and increase serum insulin levels [35].

A Case-control study has shown an inverse relationship between intake of vitamin D supplements or cod liver oil (a major source of vitamin D in certain countries) during infancy and development of type 1 diabetes mellitus [36]. Cod-liver oil has a very high vitamin D content. Regular vitamin D supplementation of 50 mg/d during infancy in the 1960s was associated with a markedly reduction in the risk of type 1 diabetes 30 years later in comparison with unsupplemented infants. In a more recent cohort, children suspected of having rickets during the first year of life had a threefold increased prevalence of type 1 diabetes in comparison with those without such a suspicion [37]. In Germany, the incidence of type 1 diabetes in adolescents is higher in autumn and winter compared with spring and summer [38]. Autoimmune processes are regarded to play an important role in the pathogenesis of type 1 diabetes. Again, it should be mentioned that calcitriol has immunomodulatory properties. Availability of calcitriol in the cell may thus influence autoimmune processes. The vitamin D hypothesis is also in line with results demonstrating that the risk of type 1 diabetes and of type 2 diabetes is influenced by the VDR genotype at the *Bms*I restriction site [39, 40]. It should be mentioned that hypertension, cardiovascular diseases, and diabetes mellitus are often associated with obesity. Obese subjects have an increased risk for low circulating 25(OH)D levels [41, 42] due to the storage of vitamin D and 25(OH)D in adipose tissue [42]. The alterations in vitamin D metabolism of obese subjects in comparison with lean subjects are also associated with functional alterations such as elevated PTH levels [41, 42]. Obesity might thus contribute to insufficient circulating 25(OH)D levels. Insulin resistance has been described in several diseases that increase cardiovascular risk and mortality, such as diabetes, obesity, hypertension, metabolic syndrome, and heart failure.

Vitamin D and immuno-modulation of gestational diabetes. Besides kidney, the placenta appears to be the most abundant source of *CYP27B1* expression, a gene responsible for coding the enzyme 25(OH)D-1-α-hydroxylase for converting the circulating form of vitamin D (25-hydroxyvitamin D) to the active form ($1,25(OH)_2D$). This unique placental capacity to synthesize active $1,25(OH)_2D$ has been linked to an immunomodulatory function for placental *CYP27B1* in humans [43]. It is highly likely that the local synthesis of $1,25(OH)_2D$ in the placenta triggers a novel anti-inflammatory target. Placental expression of this gene *CYP27B1* in humans is induced early in gestation (Fig. 3). In humans, the enzyme is strongly expressed in both maternal decidual cells and fetal trophoblastic cells, but is also detectable in decidual macrophages [44]. *In vitro*, $1,25(OH)_2D$ has been shown to suppress IFNγ production by T-cells as part of its modulatory effects on T-cell phenotype [45]. Thus *CYP27B1* may influence placental IFNγ as a consequence of impaired local synthesis of suppressive $1,25(OH)_2D$. Over-abundance of IFNγ, a type T-helper cell (Th1) cytokine, has been linked to recurrent spontaneous fetal abortion in humans [46]. In view of the well-recognized ability of $1,25(OH)_2D$ to promote transition from Th1 activity to more tolerant Th2 responses [47], it is tempting to speculate that loss of $1,25(OH)_2D$ synthesis by the placenta may contribute to a less favorable immune environment during pregnancy.

Placental expression of inflammatory cytokines is part of normal immune function during pregnancy [48], but excessive cytokine responses are also known to play a key role in adverse outcomes of pregnancy

[49–52], suggesting a «fine tuning» implemented by $1,25(OH)_2D$.

Vitamin D receptors are present in pancreatic B cells, and vitamin D may augment insulin secretion and insulin sensitivity [53] suggesting an endocrine role of vitamin D in GDM. Insufficient or deficient levels of vitamin D may allow diabetic insult at later stages in gestation leading to gestational diabetes and changes in a variety of key functional molecules including gene expression [10]. The hormone is capable of modulating the expression of a very large number of genes, possibly up to 10 % of the genome [54]. Moreover, recent reports demonstrating direct effects of $1,25(OH)_2D$ on the generation of regulatory T-cells [55], suggest that impaired synthesis of this hormone in the placenta may have wider consequences for immune responses during pregnancy, even in the absence of a pathogenic challenge.

This may lead to creating a diabetic environment comprised of a network of substances (hormones, nutrients, cytokines) with altered concentrations (Fig. 1).

Conclusions. It appears that vitamin D insufficiency during pregnancy (or even pre-pregnancy), is potentially associated with increased risk of insulin resistance and gestational diabetes mellitus. It seems plausible that the rising incidence of diabetes mellitus might be partly due to the suboptimal vitamin D status of the population. The evidence from animal and observational human studies is compelling; however, because vitamin D is an excellent marker of general health status, the positive results reported in the observational studies might reflect unmeasured and unaccounted confounding.

Furthermore, experimental data also anticipate that vitamin D sufficiency is critical for fetal development, and especially for fetal brain development and immunological functions. Vitamin D deficiency during pregnancy may, therefore, not only impair maternal skeletal preservation and fetal skeletal formation but also be pivotal to expression of multiple genes during pregnancy, imprinting the health of fetus later in life. Although the existing physiological evidence of GDM points towards a causal relationship with vitamin D, its definite involvement is unclear. Vitamin D status assessments in large cohorts with GDM, both pre-pregnancy and during pregnancy are required. Also, vitamin D supplementation in randomized clinical trials to assess the specific outcome of pregnancy and overall maternal and fetal health are essential.

Чандер П. Арора

Роль вітаміну D у модуляції гестаційного цукрового діабету

Резюме

Низький рівень основної циркулюючої форми вітаміну D у вагітних може бути фактором, що викликає прояв гестаційного цукрового діабету (ГСД). Недостатній рівень або дефіцит вітаміну D може спричинити діабетичний інсульт під час вагітності і призвести до ГСД, а також, як наслідок, до змін у функціонуванні різних ключових молекул та експресії генів. Аутокринний метаболізм вітаміну D підвищує протизапальну відповідь на децидуальну оболонку і трофобласт. Імуномодулювальна дія вітаміну D може бути нівельована за умов його низького рівня і супроводжуватися негативними фізіологічними наслідками. Останні дані демонструють, що ауто- і паракринний вплив вітаміну D у вагітних здатний одночасно підвищувати стійкість до інсуліну і знижувати секрецію останнього, пов'язану із запаленнями та метаболічними розладами у матері. Інсулін і цитокіни забезпечують основний внесок у каскад подій та виступають потенційними регуляторами плацентарної функції при ГСД. Ця стаття покликана висвітлити результати вивчення можливих механізмів, що лежать в основі ГСД, які, вірогідно, регулюються плейотропними ефектами вітаміну D.

Ключові слова: вітамін D, гестаційний цукровий діабет, плацента, інсулін, імунна відповідь.

Чандер П. Арора

Роль витамина D в модуляции гестационного сахарного диабета

Резюме

Низкий уровень основной циркулирующей формы витамина D у беременных может быть фактором, вызывающим проявление гестационного сахарного диабета (ГСД). Недостаточный уровень или дефицит витамина D может стать причиной диабетического инсульта во время беременности и приводить к ГСД, а также, как следствие, к изменению функционирования различных ключевых молекул и экспрессии генов. Аутокринный метаболизм витамина D повышает противовоспалительный ответ на децидуальную оболочку и трофобласт. Иммуномодулирующее влияние витамина D может быть нивелировано в условиях его низкого уровня и сопровождаться отрицательными физиологическими последствиями. Последние данные показывают, что ауто- и паракринное действие витамина D у беременных способно одновременно повышать устойчивость к инсулину и снижать секрецию последнего, связанную с воспалениями и метаболическими расстройствами у матери. Инсулин и цитокины вносят основной вклад в каскад событий и являются потенциальными регуляторами плацентарной функции при ГСД. В этой статье представлены результаты изучения возможных механизмов, лежащих в основе ГСД, которые могут регулироваться плейотропными эффектами витамина D.

Ключевые слова: витамин D, гестационный сахарный диабет, плацента, инсулин, иммунный ответ.

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