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CORRELATION AND PATHOGENETIC INTERRELATIONS OF IMMUNOBIOCHEMICAL MARKERS IN PRIMARY IDIOPATHIC MALE INFERTILITY

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XULOSA

Dolzarbligi. *Birlamchi idiopatik erkaklar bepushtligi zamonaviy andrologiyaning eng dolzarb muammolaridan biri bo‘lib, uning patogenezi ko‘p omilliligi va fertillik buzilishining aniq sabablari yetarlicha aniqlanmaganligi bilan tavsiflanadi. Reproduktiv disfunksiya rivojlanishida surunkali yallig‘lanish, oksidativ stress, endotelial disfunksiya va metabolik buzilishlar muhim ahamiyat kasb etadi.*

Tadqiqot maqsadi. *Birlamchi idiopatik erkaklar bepushtligiga chalingan bemorlarda reproduktiv disfunksiya rivojlanishining asosiy patogenetik mexanizmlarini aniqlash maqsadida immunobiokimyoviy, metabolik, qon-tomir va reproduktiv ko‘rsatkichlar o‘rtasidagi korrelyatsion bog‘liqliklarni o‘rganish.*

Materiallar va usullar. *Tana vazni indeksi bo‘yicha guruhlarga ajratilgan 66 nafar birlamchi idiopatik erkaklar bepushtligi bilan og‘rigan bemor tekshirildi. Barcha bemorlarda spermogramma, gormonal, metabolik va immunobiokimyoviy ko‘rsatkichlar baholanib, olingan ma’lumotlar o‘rtasidagi bog‘liqlik Pirson korrelyatsiya tahlili yordamida o‘rganildi.*

Tadqiqot natijalari. *Yallig‘lanish sitokinlari, oksidativ stress va spermatogenez ko‘rsatkichlari o‘rtasida ishonchli korrelyatsion bog‘liqliklar aniqlandi. TNF-α, IL-18 va MCP-1 darajalarining oshishi spermatozoidlar konsentratsiyasi, harakatchanligi va morfologik ko‘rsatkichlarining yomonlashuvi bilan bog‘liq bo‘lsa, D vitamini yetishmovchiligi va endotelial disfunksiya yallig‘lanish hamda metabolik buzilishlarning kuchayishi bilan kechdi.*

Xulosalar. *Birlamchi idiopatik erkaklar bepushtligi yallig‘lanish, oksidativ stress, metabolik va qon-tomir buzilishlarining o‘zaro bog‘liq patologik jarayonlari bilan tavsiflanadi. Immunobiokimyoviy markerlarni kompleks baholash kasallikning patogenetik mexanizmlarini chuqurroq aniqlash va diagnostika samaradorligini oshirish imkonini beradi.*

Kalit so‘zlar: *idiopatik erkaklar bepushtligi, TNF-α, IL-18, oksidativ stress, endotelial disfunksiya, spermatogenez, insulinrezistentlik, immunobiokimyoviy markerlar, D vitamini.*

РЕЗЮМЕ

Актуальность. *Первичное идиопатическое мужское бесплодие остаётся одной из наиболее актуальных проблем современной андрологии вследствие многофакторности патогенеза и отсутствия чётко установленных причин нарушения фертильности. Особое значение в развитии репродуктивной дисфункции имеют воспаление, оксидативный стресс, эндотелиальная дисфункция и метаболические нарушения.*

Цель исследования. *Изучить корреляционные взаимосвязи между иммунобиохимическими, метаболическими, сосудистыми и репродуктивными показателями у мужчин с первичным идиопатическим бесплодием для выявления ключевых механизмов развития репродуктивной дисфункции.*

Материал и методы исследования. *Обследовано 66 мужчин с первичным идиопатическим бесплодием, распределённых по группам в зависимости от индекса массы тела. Проведены анализ спермограммы, исследование гормонального, метаболического и иммунобиохимического статуса с последующим корреляционным анализом по Пирсону.*

Результаты исследования. *Установлены значимые корреляции между провоспалительными цитокинами, оксидативным стрессом и нарушениями сперматогенеза. Повышение уровней TNF-α, IL-18 и MCP-1 ассоциировалось со снижением концентрации, подвижности и морфологии сперматозоидов, тогда как дефицит витамина D и эндотелиальная дисфункция сопровождались усилением воспалительных и метаболических нарушений.*

Выводы. *Первичное идиопатическое мужское бесплодие характеризуется взаимосвязанными воспалительными, оксидативными, метаболическими и сосудистыми нарушениями. Комплексная оценка иммунобиохимических маркеров позволяет более полно определить патогенетические механизмы заболевания и повысить эффективность диагностики.*

Ключевые слова: *идиопатическое мужское бесплодие, TNF-α, IL-18, оксидативный стресс, эндотелиальная дисфункция, сперматогенез, инсулинорезистентность, витамин D.*

Currently, idiopathic male infertility is considered one of the most complex and poorly studied forms of reproductive pathology, accounting for a significant share in the structure of male infertility. Despite the widespread introduction of modern diagnostic methods, in a significant number of patients the causes of fertility disorders remain unknown, which significantly complicates the choice of pathogenetically based therapy.

Modern research indicates the important role of chronic low-intensity inflammation, oxidative stress, endothelial dysfunction and metabolic disorders in the development of subclinical damage to the spermatogenic epithelium [1,3,6,9]. Particular importance is attached to the study of pro-inflammatory cytokines, intercellular adhesion molecules and the antioxidant system involved in the regulation of testicular microcirculation and spermatogenesis processes [2,5,8]. At the same time, the mechanisms of interaction between immunological, vascular and metabolic factors in idiopathic infertility remain insufficiently studied, which determines the relevance of further research in this area.

In recent years, increasing attention has been paid to the role of excess body weight and insulin resistance in the development of male reproductive dysfunction. It has been established that metabolic disorders are accompanied by increased production of proinflammatory cytokines, activation of lipid peroxidation processes and impaired endothelial function, which contributes to damage to Sertoli and Leydig cells [4,7,10]. Increased levels of TNF-α, IL-18 and MCP-1 are considered one of the key mechanisms in the formation of a chronic inflammatory response and destabilization of the testicular microenvironment [11,12]. At the same time, a decrease in the activity of antioxidant enzymes leads to the accumulation of reactive oxygen species and damage to sperm membranes [13]. However, most existing studies evaluate individual pathogenetic links in isolation, while a comprehensive correlation analysis of the relationships between immunobiochemical, metabolic and reproductive indicators remains insufficiently developed, which determines the need to study the systemic relationships between the markers under study for a deeper understanding of the pathogenesis of idiopathic male infertility.

MATERIALS AND METHODS OF RESEARCH

The study included 66 men with primary idiopathic infertility undergoing examination in a specialized andrology department. Based on their body mass index, patients were divided into two groups: Group I, men with normal body weight (n=39), and Group II, men with overweight (n=27). Inclusion criteria included a history of pregnancy within 12 months of regular unprotected sexual intercourse, the absence of significant organic reproductive system pathology, and the presence of idiopathic infertility after standard clinical and laboratory testing.

All patients underwent a clinical examination, sperm analysis according to WHO criteria (2021), hormonal profile, lipid and carbohydrate metabolism, coagulation profile, and immunobiochemical markers of inflammation, oxidative stress, and endothelial dysfunction. Levels of TNF-α, IL-18, MCP-1, VEGF, endothelin-1, ICAM-1, VCAM-1, superoxide dismutase (SOD), oxidative stress indicators, vitamin D, lipid profile, glucose, insulin, and the HOMA-IR index were determined. Biochemical parameters of sperm plasma, including zinc, fructose, and citric acid levels, were analyzed.

To assess systemic relationships between the studied parameters, a correlation analysis was conducted using the Pearson correlation coefficient (r). Statistical processing of the data was performed using the Statistica 10.0 software package. Differences were considered statistically significant at $p < 0.05$.

RESEARCH RESULTS

A comparative analysis of immunobiochemical markers in groups of patients with normal and overweight body weight revealed a consistent trend in their changes, characterized by increased levels of proinflammatory cytokines, markers of endothelial dysfunction, and oxidative stress, along with a decrease in antioxidant defense. However, the differences between the groups were primarily quantitative rather than qualitative.

In this regard, to assess the systemic relationships between the studied indicators, a correlation analysis was performed in a pooled sample of patients, which made it possible to increase the statistical power of the study and identify common pathogenetic patterns.

Table 1

Correlation links between immunobiochemical markers and spermogram

Indicator	TNF-α	IL-18	OS	SOD	Movementnost	Morphology	Concenttraction
TNF-α	1	0.62	0.58	-0.55	-0.56	-0.48	-0.51
IL-18	0.62	1	0.54	-0.49	-0.50	-0.49	-0.47
OS	0.58	0.54	1	-0.61	-0.52	-0.46	-0.52
SOD	-0.55	-0.49	-0.61	1	0.48	0.42	0.44
Mobility	-0.56	-0.50	-0.52	0.48	1	0.58	0.55
Morphology	-0.48	-0.49	-0.46	0.42	0.58	1	0.52
Concentration	-0.51	-0.47	-0.52	0.44	0.55	0.52	1

Correlation analysis demonstrated the presence of stable negative relationships between proinflammatory cytokines and the main parameters of spermatogenesis. TNF-α levels had a significant negative correlation with sperm motility (r=-0.56), indicating a decrease in their functional activity with an increased inflammatory response. This effect may be due to the ability of TNF-α to induce mitochondrial dysfunction, which leads to a decrease in the energetic potential of sperm. Furthermore, TNF-α is involved in the activation of apoptotic cascades, which can lead to the death of spermatogenic cells. A similar negative correlation between IL-18 and sperm morphology (r=-0.49) indicates a disruption in spermatid differentiation processes. IL-18 enhances the

production of other proinflammatory cytokines, which contributes to the destabilization of the testicular tissue microenvironment. Oxidative stress showed negative correlations with sperm concentration and motility (r=-0.52), reflecting damage to cell membranes and DNA. Reactive oxygen species induce lipid peroxidation, disrupting membrane integrity (Table 1). Superoxide dismutase, on the other hand, showed positive correlations with sperm motility and concentration, confirming its protective role. A decrease in SOD leads to the accumulation of free radicals and exacerbation of sperm damage. The combination of these relationships reflects a key link in the pathogenesis–oxidative-inflammatory damage to spermatogenesis.

Table 2

Correlation between immunobiochemical markers and lipid spectrum

Indicator	TNF-α	IL-18	OS	SOD	LDL	HDL	Atherosclerosis index genes
TNF-α	1	0.60	0.57	-0.52	0.51	-0.45	0.54
IL-18	0.60	1	0.53	-0.48	0.47	-0.41	0.49
OS	0.57	0.53	1	-0.59	0.50	-0.46	0.53
SOD	-0.52	-0.48	-0.59	1	-0.44	0.44	-0.47
LDL	0.51	0.47	0.50	-0.44	1	-0.52	0.66
HDL	-0.45	-0.41	-0.46	0.44	-0.52	1	-0.61
Atherogenic index	0.54	0.49	0.53	-0.47	0.66	-0.61	1

The identified correlations indicate a close integration of inflammatory and metabolic processes. A positive association between TNF-α and LDL (r = 0.51) indicates increased inflammation with an increase in atherogenic lipid fractions. Oxidized LDL can activate macrophages, increasing the production of proinflammatory cytokines. The correlation between IL-18 and total cholesterol reflects the involvement of lipid metabolism in the regulation of the immune response. Elevated cholesterol contributes to the development of a proinflammatory phenotype. The oxidative stress index had a significant relationship with the atherogenicity index (r = 0.53), indicating increased lipid peroxidation. Lipid peroxidation leads to damage to cellular structures. SOD demonstrated a positive association with HDL, reflecting the antioxidant properties of high-density lipoproteins (Table 2). HDL can neutralize free radicals and reduce inflammation. Negative correlations between HDL and inflammatory markers confirm their protective role. This leads to metabolically mediated inflammation, which impacts reproductive function.

Table 3

Correlations between immunobiochemical markers and carbohydrate metabolism indices

Indicator	TNF-α	MCP-1	OS	SOD	Glucose	Insulin	HOMA-IR
TNF-α	1	0.58	0.56	-0.52	0.48	0.55	0.58
MCP-1	0.58	1	0.53	-0.49	0.46	0.52	0.54
OS	0.56	0.53	1	-0.60	0.46	0.50	0.52
SOD	-0.52	-0.49	-0.60	1	-0.41	-0.47	-0.49
Glucose	0.48	0.46	0.46	-0.41	1	0.62	0.66
Insulin	0.55	0.52	0.50	-0.47	0.62	1	0.72
HOMA-IR	0.58	0.54	0.52	-0.49	0.66	0.72	1

Correlation analysis revealed that carbohydrate metabolism parameters are closely linked to immunobiochemical markers. A positive correlation between TNF-α and HOMA-IR (r = 0.58) suggests a link between inflammation and insulin resistance (Table 3). TNF-α can inhibit insulin receptors, disrupting intracellular signaling. MCP-1 demonstrated a positive relationship with insulin levels, reflecting the activation of macrophages in adipose tissue, which leads to increased chronic inflammation. The OS indicator correlated with glucose levels, indicating the effect of hyperglycemia on the intensification of free radical processes. Glucose promotes the formation of reactive oxygen species through protein glycation. SOD had a negative correlation with HOMA-IR, reflecting a decrease in antioxidant protection in metabolic disorders. Insulin resistance increases oxidative stress, creating a mutually reinforcing process. These relationships confirm the key role of insulin resistance in pathogenesis.

Table 4

Correlations between immunobiochemical markers and coagulogram parameters

Indicator	TNF-α	MCP-1	Fibrinogen
TNF-α	1	0.57	0.55
MCP-1	0.57	1	0.51
Fibrinogen	0.55	0.51	1

The analysis revealed significant links between inflammatory markers and the hemostatic system. A positive correlation between TNF-α and fibrinogen (r = 0.55) indicates activation of the coagulation pathway during inflammation. TNF-α stimulates fibrinogen synthesis in the liver. MCP-1 also demonstrated a link with fibrinogen, reflecting the involvement of chemokines in coagulation processes (Table 4). Elevated fibrinogen increases blood viscosity, leading to impaired microcirculation. Hypoxic conditions develop in testicular tissue. Hypoxia aggravates damage to the spermatogenic epithelium. The relationship between inflammation and coagulation confirms the presence of a vascular component in pathogenesis. This mechanism plays an important role in disease progression.

Table 5

Correlation relationships between immunobiochemical markers and sperm plasma parameters

Indicator	OS	TNF-α	IL-18	Zinc	Fructose	Citric acid
OS	1	0.56	0.52	-0.50	-0.45	-0.48
TNF-α	0.56	1	0.60	-0.46	-0.46	-0.44
IL-18	0.52	0.60	1	-0.48	-0.43	-0.48
Zinc	-0.50	-0.46	-0.48	1	0.51	0.49
Fructose	-0.45	-0.46	-0.43	0.51	1	0.58
Citric acid	-0.48	-0.44	-0.48	0.49	0.58	1

Significant relationships were found between inflammatory markers and the biochemical composition of the sperm plasma. The OS indicator had a negative correlation with the zinc level (r = -0.50), reflecting a decrease in antioxidant protection. Zinc is a cofactor for antioxidant enzymes. Its deficiency increases sperm damage. TNF-α demonstrated a negative relationship with fructose, indicating a disruption of energy metabolism (Table 5). Fructose is the main energy substrate for sperm. IL-18 also correlated with citric acid, reflecting a disruption of the secretory function of the prostate gland. Positive correlations between the components of the sperm plasma indicate their functional interrelationship. Disruption of one link leads to changes in others, resulting in local damage to the testicular environment.

Table 6

Correlations between vitamin D and immunobiochemical markers

Indicator	Vit D	TNF-α	IL-18	SOD
Vit D	1	-0.54	-0.50	0.47
TNF-α	-0.54	1	0.60	-0.52
IL-18	-0.50	0.60	1	-0.48
SOD	0.47	-0.52	-0.48	1

Vitamin D demonstrated significant relationships with inflammatory and antioxidant parameters. A negative correlation with TNF-α (r = -0.54) indicates its anti-inflammatory role. Vitamin D inhibits the production of proinflammatory cytokines. A similar relationship with IL-18 confirms its role in regulating the immune response. A positive correlation with SOD reflects its influence on the antioxidant system. Vitamin D promotes the activation of antioxidant enzymes (Table 6). Its deficiency leads to increased inflammation (Table 6), which is accompanied by increased oxidative stress. Immune dysregulation develops. This factor exacerbates the pathological process.

Table 7

Correlations between BMI, systemic parameters and sperm motility

Indicator	BMI	TNF-α	OS	SOD	Mobility
BMI	1	0.59	0.56	-0.52	-0.61
TNF-α	0.59	1	0.58	-0.55	-0.56
OS	0.56	0.58	1	-0.61	-0.52
SOD	-0.52	-0.55	-0.61	1	0.48
Mobility	-0.61	-0.56	-0.52	0.48	1

Body mass index demonstrated a central role in the development of pathological relationships. A positive correlation with TNF-α (r = 0.59) indicates increased inflammation with increasing adipose tissue. Adipocytes actively produce proinflammatory cytokines. The relationship between BMI and oxidative stress reflects increased free-radical processes. Adipose tissue is a source of oxidative reactions. A negative correlation with SOD indicates a decrease in antioxidant protection. A negative correlation with sperm motility was also found (r = -0.61) (Table 7). The obtained data indicate the influence of metabolic disorders on reproductive function. BMI acts as an integrating factor in pathogenesis. Its increase triggers a cascade of pathological changes.

Table 8

Correlation analysis of immunobiochemical markers

Indicator	EN-1	VEGF	OS	SOD	ICAM-1	VCAM-1	MCP-1	TNF-α	IL-18
EN-1	1	0.58	0.55	-0.52	0.56	0.53	0.50	0.57	0.54
VEGF	0.58	1	0.52	-0.48	0.54	0.56	0.49	0.53	0.51
OS	0.55	0.52	1	-0.61	0.57	0.55	0.53	0.58	0.56
SOD	-0.52	-0.48	-0.61	1	-0.50	-0.48	-0.46	-0.55	-0.52
ICAM-1	0.56	0.54	0.57	-0.50	1	0.62	0.58	0.60	0.57
VCAM-1	0.53	0.56	0.55	-0.48	0.62	1	0.56	0.58	0.55
MCP-1	0.50	0.49	0.53	-0.46	0.58	0.56	1	0.59	0.57
TNF-α	0.57	0.53	0.58	-0.55	0.60	0.58	0.59	1	0.63
IL-18	0.54	0.51	0.56	-0.52	0.57	0.55	0.57	0.63	1

An analysis of correlations between immunobiochemical markers demonstrated the formation of a single interconnected system reflecting the complex involvement of inflammatory, endothelial, and oxidative mechanisms. Endothelin-1 was found to have positive correlations with VEGF (r = 0.58), ICAM-1 (r = 0.56), and TNF-α (r = 0.57), indicating a close association between endothelial dysfunction and inflammatory processes. These relationships indicate that impaired vascular tone is accompanied by activation of cellular adhesion and the cytokine response. VEGF demonstrated positive correlations with ICAM-1 and VCAM-1, reflecting the coupling of angiogenesis and endothelial activation processes, suggesting that compensatory angiogenesis develops against the background of inflammatory damage to the vascular wall.

The oxidative stress indicator had the most pronounced correlations with TNF-α (r = 0.58), IL-18 (r = 0.56), and ICAM-1 (r = 0.57), indicating a close integration of free radical processes with the inflammatory response. An increase in OS is accompanied by activation of the cytokine cascade and increased cell adhesion. At the same time, SOD demonstrated inverse correlations with virtually all markers, including TNF-α (r = -0.55) and OS (r = -0.61), confirming its key role in antioxidant defense. A decrease in SOD activity is accompanied by an increase in damaging processes.

The relationships between adhesion molecules and cytokines are particularly noteworthy. ICAM-1 and VCAM-1 were strongly correlated (r = 0.62), suggesting coordinated endothelial activation. Their association with TNF-α (r = 0.60) suggests a role for cytokines in the induction of adhesion molecules. MCP-1 also demonstrated significant associations with TNF-α and ICAM-1, reflecting the involvement of chemotactic mechanisms.

The strongest correlation was found between TNF-α and IL-18 (r=0.63), reflecting the synergism of proinflammatory cytokines. Their combined increase in activity intensifies the inflammatory cascade (Table 8), leading to damage to cellular structures and disruption of intercellular interactions. The relationship between these markers indicates the central role of inflammation.

DISCUSSION OF THE RESEARCH RESULTS

A correlation analysis revealed close links between inflammatory, metabolic, endothelial, and reproductive parameters in men with primary idiopathic infertility. The results indicate the development of a unified, multilevel pathological cascade, underpinned by the combined effects of chronic inflammation, oxidative stress, and metabolic dysregulation.

According to our data, the TNF-α level had a significant negative correlation with sperm motility (r=-0.56), sperm morphology, and sperm concentration. Similar results were presented by Tremellen (2008), who showed that an increase in proinflammatory cytokines is accompanied by impaired sperm mitochondrial function and increased apoptosis of spermatogenic cells [10]. Our data are also consistent with the studies of Agarwal et al. (2021), indicating the leading role of oxidative-inflammatory damage in impaired spermatogenesis [1].

The identified relationships between oxidative stress indicators and spermogram parameters deserve special attention. In our study, oxidative stress negatively correlated with sperm concentration and motility, while superoxide dismutase demonstrated positive correlations with the main parameters of spermatogenesis. Similar results were obtained by Sharma et al. (2013), who showed that a decrease in the activity of the antioxidant system is accompanied by damage to sperm membranes and fragmentation of their DNA [9]. According to Leisegang et al. (2021), increased free radical processes are one of the key factors in reproductive dysfunction in metabolic disorders [7].

An analysis of metabolic relationships revealed that TNF-α and MCP-1 were positively correlated with insulin resistance and insulin levels. These results support the concept of metabolically induced chronic inflammation. Similar data were presented by Craig et al. (2017), who indicated that insulin resistance is accompanied by activation of adipose tissue macrophages and increased production of proinflammatory cytokines [4]. Furthermore, the positive correlation we found between body mass index and TNF-α levels confirms the important role of adipose tissue as a source of the chronic inflammatory response.

The obtained results demonstrated a close relationship between inflammatory processes and lipid metabolism disorders. In our study, TNF-α correlated positively with LDL levels and the atherogenic index, while HDL

had negative correlations with inflammatory markers. Similar data were obtained by Vander Borght and Wyns (2018), who showed that dyslipidemia contributes to the activation of lipid peroxidation processes and damage to cell membranes [11]. According to Salas-Huetos et al. (2017), lipid metabolism disorders lead to a decrease in antioxidant protection and a deterioration in sperm quality [8].

It is worth noting the correlations we identified between markers of endothelial dysfunction, cell adhesion molecules, and proinflammatory cytokines. Increased levels of ICAM-1, VCAM-1, and VEGF were accompanied by an increased inflammatory response and oxidative stress. Similar results were presented by Ilacqua et al. (2018), who considered endothelial dysfunction to be an important component of testicular microcirculation impairment in male infertility [6]. Increased vascular inflammation contributes to the development of testicular hypoxia and damage to the spermatogenic epithelium.

An important finding of the study was the negative correlation of vitamin D with TNF-α and IL-18, as well as a positive association with SOD. These findings support the anti-inflammatory and antioxidant role of vitamin D. Similar results were described by Boeri et al. (2019), who demonstrated that vitamin D deficiency is accompanied by the activation of proinflammatory cytokines and impaired reproductive function [3].

The results of the study indicate that idiopathic male infertility develops against the background of a complex interaction of inflammatory, oxidative, vascular, and metabolic disorders. The obtained correlations confirm the existence of a unified pathogenetic network in which chronic inflammation, insulin resistance, endothelial dysfunction, and oxidative stress mutually potentiate each other, leading to progressive impairment of spermatogenesis.

CONCLUSIONS

A correlation analysis revealed that primary idiopathic male infertility is characterized by a unified, interconnected system of inflammatory, metabolic, endothelial, and oxidative disturbances that negatively impact spermatogenesis. An increased proinflammatory response is accompanied by a deterioration in sperm function, decreased antioxidant defense, and altered biochemical composition of the seminal plasma. Insulin resistance, dyslipidemia, and an increase in body mass index were found to be closely linked to the activation of the cytokine cascade and oxidative stress. The development of endothelial dysfunction and microcirculation disorders contributes to chronic testicular tissue damage and the progression of reproductive dysfunction. These results confirm the multifactorial nature of the pathogenesis of idiopathic male infertility and substantiate the need for a comprehensive assessment of immunobiochemical and metabolic markers during patient examination.

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