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Evaluation the role of Trimetazidine in managing impaired fertility in rats treated with alloxan-induced hyperglycemia

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ABSTRACT

It has been shown that the chronic metabolic derangement accompanying long-standing hyperglycemia, both in experimental animals and man, may alter fertility in males. Recent reports have investigated the role of Trimetazidine in improving fertility parameters; however, the results are still controversial. This study was aimed to evaluate the role of Trimetazidine concerning fertility parameters in experimentally induced hyperglycemia in rats. Three groups of rats have subjected to alloxan induced hyperglycemia, placebo treatment (control group), and alloxan and TMZ treatment (study group). Each group included ten animals. Sperm parameters, hormonal levels, markers of oxidative stress and Histophotometry were done according to previously published literature. Sperm parameters in the form of sperm count, normal morphology, motility and number of dead sperms were significantly altered following alloxan induced hyperglycemia ($P < 0.001$). The administration of TMZ showed significant improvement in sperm parameters ($P < 0.001$) in addition to significant improvement in markers of oxidative stress, GSH, SOD, MDA and NO ($P < 0.001$), and in hormonal levels, testosterone and FSH ($P < 0.001$). TMZ is useful in optimizing fertility parameters in experimental rats following alloxan induced hyperglycemia through antioxidant mechanisms and improved hormonal profile.

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INTRODUCTION

Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse"(Zhang *et al.*, 2006). Diabetes mellitus is a social affair of metabolic sicknesses depicted by steady hyperglycemia caused by distortions in insulin outflow, insulin action, or both. The metabolic varieties from the

standard of sugars, lipids, and proteins result from the hugeness of insulin as an anabolic hormone. Low elements of insulin to achieve an acceptable response as well as insulin restriction in target tissues, essentially skeletal muscle, fat tissue and, to a lesser degree, the liver, at the element of insulin, signal transduction structure and additionally impetuses or effectors characteristics (Kharroubi, 2015). They are accountable for these metabolic varieties from the standard. The mammalian is the most isolated mammalian. The essential inspiration driving sperm is to trade the male haploid-DNA to female DNA through the movement of parts including its evacuation along the female genital tract and its ability to get ready. Sperm imperativeness is generally used to keep up the motility basic for the course of action and the back acrosome reaction (Agarwal & Said, 2005). In any case, a sporadic circumstance, for instance, diabetes can incite supplement transport brokenness, realizing lessened readiness and ominous effects on the infant (Civelek *et al.*, 2014). A previous discussion on the explana-

tion of GLUT8 and GLUT9 in the sperm and gonads of two genetically balanced, genetically balanced and genetically balanced mice revealed that mice lacking the GLUT9 protein had low sperm motility and reduced treatment. The lack of assistance with insulin or hyperglycemia alters the understanding of Glut9 and explains why insulin and glucose expect a basic use of sperm development and accept a basic occupation to improve motor control of sugar sperm. Means of planning and treatment (Balercia *et al.*, 2004). In addition, when these comparable mice were treated with insulin, the adaptability and the concentrate were extended, suggesting that the activation of insulin improves sperm quality. Likewise, it has been found that glucose, and not fructose, is essential for treatment and is unequivocally necessary for the relationship between sperm and the common sense of life creation in mice (Aziret *et al.*, 2014). Trimetazidine is a cytoprotective drug that measures the effects of the metabolic agitator in low-speed hemiplegics through the various segments of the movement that are still exchanging (First & Paper, 2017). The instrument of action of trimethylamine is the limit of the β -oxidation of free unsaturated fats (FFA) (Kantor *et al.*, 2000). In the tests, TMZ was tempted by the operator to anticipate the illness of the store. The rat evaluated the effect of this after the exploratory list of hyperglycemia (Kharroubi, 2015). The association of perfect TMZ anchors against the effects of rodent hyperglycemia and the treatment of TMZ can be used to maintain classical spermatogenesis by diabetic extensions. The proposed part is that the cellular support of TMZ decreases the toxic effect of free radicals in sperm and that, indirectly, the number, morphology, and motility of sperm of what remains of average diabetes are related to TMZ. Estimates have become familiar with the variety of norms related to the number, morphology, and motility of sperm (Aziret *et al.*, 2014).

MATERIALS AND METHODS

Fifty sounds, research centre reared, male, pale skinned person rodents weighing 200-300gm. were utilized, age 8-12 weeks' old were acquired from the Iraqi focus of medication assessment and research. Kept up under standard research centre conditions, for example, 12-hour light/dull cycle and they were nourished standard rat pellet diet, and they have free access to water. The animals were housed in box cages of opaque plastic measuring (45x30x15) cm. Cages floor was covered with a wooden shave. Experimental rats were examined during the experiment, and all abnormal rats were excluded from the study. The cages were cleaned and sterilized with 70% ethanol

every five days. The laboratory animals will be randomly divided into three groups (10 animals per group): group A (normal control group); group B (normal control group "hyperglycemic control group negative" and group C receiving saline (oral doses of Trimetazidine (5 mg / kg) per tube, between 7 hours and 9 hours per day for 10 weeks). Fasting from non-hyperglycemic control rats and hyperglycemic rats with and without intervention were estimated weekly, using a studied glucometer, the drugs administered directly after the induction of hyperglycemia (40 mg/ml) at a dose of 40 mg/kg to rats fasting overnight for two consecutive days to induce hyperglycemia. The medication was as of late arranged before organization upon the arrival of the test. Refined water, these portions were picked dependent on past investigations that have been considered in rodents. The serum centralization of LH, FSH, and testosterone was estimated utilizing an ELISA peruser utilizing business test units as per the maker's conventions. Sperm parameters included sperm check, percent portability, percent right morphology, and feasibility; the tests were precisely extracted after stomach cuts and examples were resolved. The cross segment with a thickness is "5-6 μ m" pivoting microtome. Finally, the areas were recoloured with "H and E" (Stevens *et al.*, 1982). The morph metric investigation of 20 tubes for every creature, the mean distance across of the fundamental tubules and the stature of the embryonic epithelia were resolved to utilize the program themes in addition to 2.0 ml. To assess spermatogenesis, twenty of the most adjusted channels of the testicular area were chosen and determined. The oxidative pressure markers present in the serum were assessed and included glutathione (SGH), superoxide dismutase (SOD), and nitric oxide (NO) action as per the directions of the organization giving the administrations.

RESULTS

There was no significant difference in mean weight, mean testes weight and mean ratio among control and study groups ($P > 0.235$), as shown in table 1. Sperm count and percent sperm motility were highly significantly lowest in the hyperglycemic group ($P < 0.001$), whereas, morphologically abnormal sperm % and dead sperm % were highly significantly highest in the hyperglycemic group ($P < 0.001$). No significant difference was observed in sperm parameters between control and TMZ ($P > 0.05$), table 2. Mean serum testosterone and FSH were exceedingly fundamentally most reduced in hyperglycemic gathering ($P < 0.001$). The ordinary serum testosterone and FSH levels in

Table 1: Mean body weight, testes weight and ratio among control and study groups

Characteristic	Control	Hyperglycemia	TMZ	P
Body Weight (gm)	280.40 ±25.57	278.80 ±40.30	293.50 ±15.91	0.235* NS
Testes Weight (gm)	2.73 ±0.39	2.77 ±0.21	3.09 ±0.26	0.413 NS
Testes weight/Bodyweight	117.34 ±8.81	123.68 ±19.08	115.30 ±8.99	0.413 NS

Table 2: Sperm parameters of the control and study groups

Characteristic	Control	Hyperglycemia	TMZ	P
Sperm count	26.10 ±3.38	17.70 ±3.43	25.00 ±2.45	<0.001 HS
Sperm motility %	92.00 ±2.58	67.50 ±5.89	86.50 ±7.47	<0.001 HS
Abnormal sperm %	9.10 ±2.23	16.20 ±4.98	7.30 ±2.00	<0.001 HS
Dead sperm %	8.70 ±4.55	16.10 ±5.99	6.80 ±2.49	<0.001 HS

*One-way ANOVA; SD: standard deviation; HS: Highly significant

Table 3: Mean serum testosterone in the control and study groups

Hormone level	Control	Hyperglycemia	TMZ	P*
Testosterone	2.75 ±0.92	1.60 ±1.02	4.35 ±0.61	<0.001 HS
FSH	2.39 ±0.49	1.27 ±0.25	4.19 ±0.96	<0.001 HS
LH	2.20 ±0.63	2.64 ±0.77	2.34 ±0.70	0.902 NS

*One-way ANOVA; SD: standard deviation; HS: Highly significant; NS: not significant

Table 4: Markers of oxidative stress in the control and study groups

Marker	Control	Hyperglycemia	TMZ	P*
GSH	4.24 ±0.35	2.64 ±0.36	3.90 ±0.51	<0.001 HS
SOD	17.23 ±2.46	10.16 ±2.19	20.50 ±2.98	<0.001 HS
MDA	6.43 ±0.96	15.11 ±2.02	8.94 ±0.56	<0.001 HS
NO	5.04 ±0.74	1.85 ±0.39	2.31 ±0.44	<0.001 HS

*One-way ANOVA; SD: standard deviation; HS: highly significant

TMZ was inside and out higher than in the control gathering ($p < 0.05$). There was no basic qualification in mean serum LH between the control and test social occasions ($P = 0.902$), Table 3.

Mean serum glutathione was fundamentally lower in the hyperglycemia gather than control gathering and TMZ ($P < 0.001$). There was no critical distinction in mean blood glutathione among control and temozolomide, gatherings ($P > 0.05$). The mean serum SOD focus was altogether higher in the hyperglycemic bunch than the control gathering and the TMZ gathering ($P < 0.001$). The mean estimation of TMOD serum SOD was altogether higher than the control gathering ($P < 0.05$). The mean serum MDA was fundamentally higher than the hyperglycemia gathering ($P < 0.001$). The normal MDA serum in TMZ was essentially lower than the hyperglycemic gathering. In any case, it was essentially higher than the control gathering ($P < 0.05$). Mean serum NO focuses were fundamentally lower in the hyperglycemic gathering ($P < 0.001$). Mean a number of NO serum in the TMZ gather was altogether higher than the hyperglycemic gathering ($P < 0.05$) and not exactly in the control gathering ($P < 0.05$), Table 4.

Mean some seminiferous tubules were generally lessened after alloxan incited hyperglycemia in a relationship with control gathering ($P < 0.05$). TMZ treated rodents seemed close average mean some

seminiferous tubules without basic refinement in a relationship with control gathering ($P > 0.05$) and through and through higher mean count in the examination with hyperglycemia gathering ($P < 0.05$). Mean size of seminiferous tubules was inside and out reduced after alloxan prompted hyperglycemia in a relationship with control gathering ($P < 0.05$). TMZ treated rodents demonstrated imperative upgrade in size of seminiferous tubules in the examination with hyperglycemia gathering ($P < 0.05$); in any case, it remains not as much as that of control gathering ($P < 0.05$). Mean Leydig cell check was diminished after alloxan prompted hyperglycemia in connection with control gathering ($P < 0.05$). TMZ treated rodents seemed close regular Leydig cell incorporate without gigantic qualification examination with control gathering ($P > 0.05$) and through and through higher Leydig cell count in connection with hyperglycemia gathering ($P < 0.05$). Mean Sertoli cell count was diminished after alloxan incited hyperglycemia in the examination with control gathering ($P < 0.05$). TMZ treated rodents seemed close customary Sertoli cell incorporate without tremendous balance relationship with control gathering ($P > 0.05$) and inside and out higher Sertoli cell check in the examination with hyperglycemia gathering ($P < 0.05$), table 5.

Table 5: Histophotometry study

Characteristic	Control	Hyperglycemia	TMZ	P*
Size of SNT	284.80 ±12.34	186.00 ±5.18	246.40 ±9.16	<0.001 HS
Number of SNT	21.60 ±2.42	14.60 ±1.20	20.80 ±2.71	<0.001 HS
Leydig cell count	55.20 ±4.31	28.00 ±2.19	41.20 ±3.97	<0.001 HS
Sertoli cell count	28.00 ±2.61	21.20 ±1.94	25.60 ±3.14	<0.001 HS

SNT: seminiferous tubule; *One-way ANOVA; SD: standard deviation; HS: highly significant

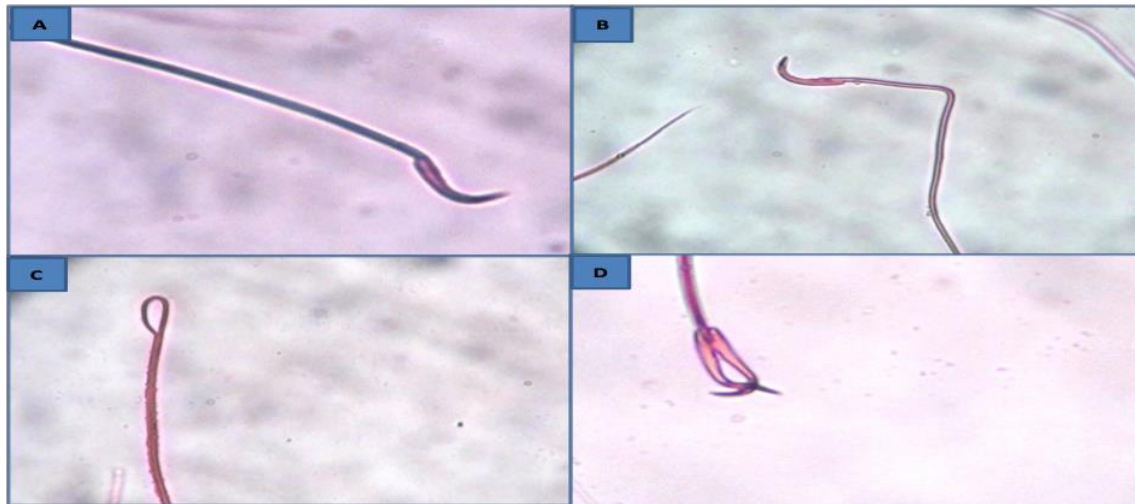


Figure 1: Photomicrograph showing normal sperm with normal head and tail regions (A); abnormal sperm with a kinked tail (B); abnormal sperm with looped tail morphology (C); abnormal sperm with double head pattern (D).

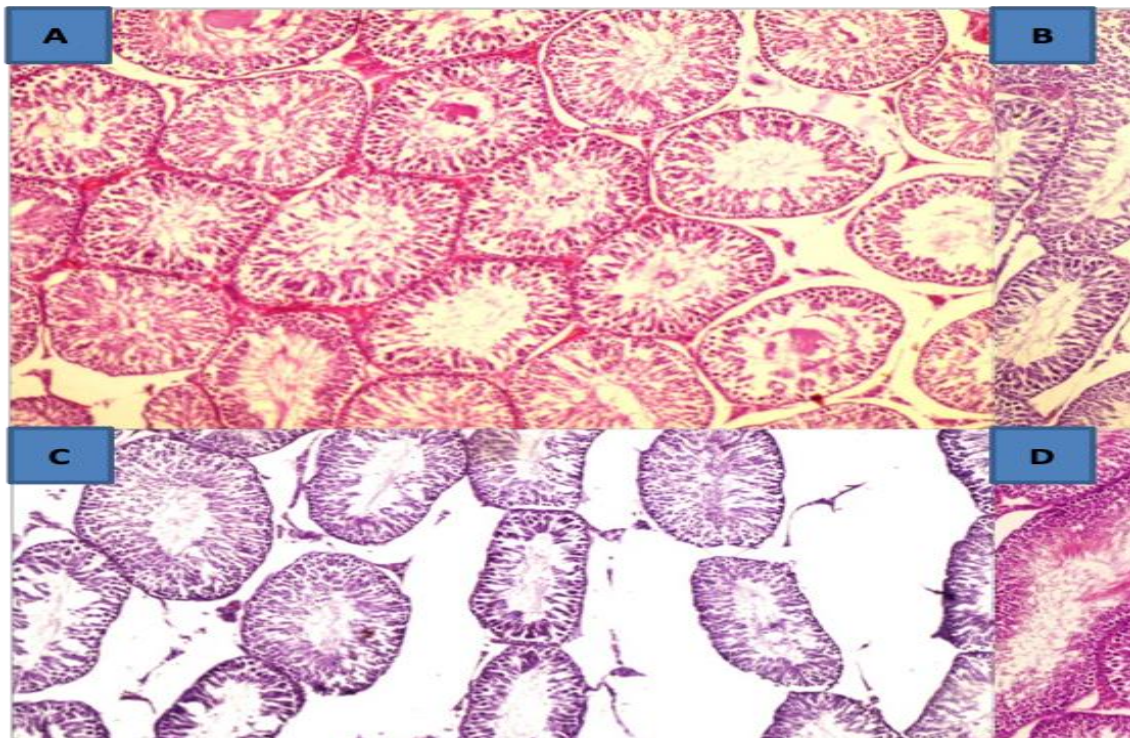


Figure 2: Section through rat testis from control group showing normal size seminiferous tubules with normal spermatogenesis (A); Section through rat testis from hyperglycemia group showing increase interstitial spaces and reduced size seminiferous tubules with normal spermatogenesis (B); Section through rat testis from hyperglycemia group showing increase interstitial spaces and variation in size of seminiferous tubules with normal spermatogenesis (C); Section through rat testis from hyperglycemia group showing increase interstitial spaces and Leydig cell hyperplasia and reduced size seminiferous tubules with normal spermatogenesis (D); (20X)H & E stain (20X).

DISCUSSION

This investigation demonstrated that alloxan-prompted hyperglycemia brought about an exceptionally critical decrease in the quantity of sperm from research facility creatures contrasted with the control gathering and that TMZ treatment was extremely compelling in normalizing (expanding) the number of spermatozoa in the creatures of the gatherings considered. Numerous models of diabetes in creatures and patients with diabetes in people have issues with spermatogenesis and fruitfulness. Diabetes is connected with lessened sperm parameters in impacted men. It isn't yet sure whether the mischief is a result of adjacent effects of hyperglycemia or changes in hormone levels exasperating the hypothalamic-pituitary-gonadal turn (Gomez O *et al.*, 2009). A couple of makers have attested that by certifying the outcomes of this examination, likely prompted hyperglycemia in the rat achieved an important abatement in sperm. The decreased sperm tally might be because of oxidative harm influencing the uprightness of sperm through assaulting sperm plasma layer. Oxidative harm is outstanding in diabetes patients (Kharroubi, 2015) Both diabetic men and knockout mice had prominently disabled spermatogenesis, expanded germ cell exhaustion, and Sertoli cell vacuolization, recommending that insulin may have an imperative job in spermatogenesis (Baccetti *et al.*, 2002). It is as yet hazy whether the impacts of diabetes on male fruitfulness are intervened through testicular insulin deficiency or foundational impacts of diabetes. Various investigations help the job of ROS in male barrenness hypothesis (Lafuente *et al.*, 2013). The structure of the plasma film is remarkable and comprises of elevated amounts of polyunsaturated unsaturated fats (PUFAs) that enhance layer adaptability. It makes sperm powerless against be assaulted by ROS. Lipid peroxidation course can truly bargain the useful respectability of layer cells, diminish sperm motility, and accordingly lessen richness. ROS creation pathologically results in elevated amounts of DNA harm that is related to properties of the mitochondrial film with loss of cells (Zhang *et al.*, 2006). In bolster for the expanded oxidative worry in actuated hyperglycemia, the current investigation indicated a critical decrease in mean GSH focus in rodents experiencing alloxan initiated hyperglycemia and GSH is known to be a strong cancer prevention agent, what's more this examination demonstrated noteworthy increment in MDA and SOD which are notable for their job in oxidative stress. Some creators demonstrated that incited hyperglycemia is related to huge ascent in oxidative pressure markers which is as per the discoveries of the current study (Al Hayek *et al.*, 2013).

On the other hand, hormonal changes owing to prompted hyperglycemia may likewise assume a job in diminished sperm check. The present investigation demonstrated that instigated hyperglycemia in rodents caused checked decrease in serum FSH and testosterone and that LH was not changed altogether. There is proof that diabetes is related to low dimensions of testosterone (Al Hayek *et al.*, 2013). It isn't known whether the low dimension of testosterone in diabetics is related to changes in luteinizing hormone (LH) and follicle invigorating hormone (FSH). Recently distributed information demonstrate that hypogonadotropic hypogonadism is the most widely recognized type of gonadal brokenness (Steg *et al.*, 2001). Low dimensions of testosterone and ordinary LH were accounted for in people with diabetes; in any case, in individuals with diabetic neuropathy, low dimensions of testosterone, elevated amounts of LH and FSH were discovered (Engle *et al.*, 2008). Organization of the ideal portion of TMZ ensures against unfriendly impacts of diabetes on spermatogenesis in rodents (Engle *et al.*, 2008). It has been suggested that the malignant growth counteractive action operator affect connected by TMZ was the basic protective instrument by which spermatogenesis was shielded in rodents with hyperglycemia. Explicitly ruins the activity of the last protein of the unsaturated fat oxidation pathway, thiolase 3-ketoacylcoyme (Agarwal & Said, 2005).

Association of this drug alters the imperativeness substrate tendencies, achieving inadequate deterrent of unsaturated fat oxidation and extended glucose oxidation. Regardless, the present examination moreover revealed that started hyperglycemia caused by alloxan was exceptionally essential. Reduced sperm motility in the dimension of research focus animals stood out from the control gathering and that TMZ treatment was on a very basic level incredible in preventing sperm rate diminish. This declaration resembles that of a couple of various makers. Lessened motility of spermatozoa may be a result of oxidative weight related with impelled hyperglycemia in the rat (Hosen *et al.*, 2015). The structure of the plasma layer is unprecedented and contains anomalous measures of polyunsaturated unsaturated fats (PUFAs) that improve the adaptability of the film (Akondi *et al.*, 2011). This makes the spermatozoa frail against ROS strikes. A lipid peroxidation course can exchange off the valuable reliability of layer cells, diminish sperm motility, and lessen productivity. Another possible elucidation is that an imperative reduction in nitric oxide may expect an occupation in decreasing the motility of spermatozoa. Men living in normozoospermic periods have been represented to have NO obses-

sions out and out lower than those of sterile men with asthenozoospermia (Balercia *et al.*, 2004). In the present examination, tantamount results were gotten in light of the way that the incited hyperglycemia achieved a lessening in sperm motility and a combination of nitric oxide. It has been prescribed that nitric oxide vitalizes sperm motility by inciting the cyclic GMP/protein kinase G pathway (Miraglia *et al.*, 2011). TMZ in this investigation has been compelling in keeping up sperm motility, and this outcome is like that of other individuals (Ozcan *et al.*, 2017). It has been recommended that the cell reinforcement impact created by TMZ is the fundamental defensive factor for motility of spermatozoa (Ozcan *et al.*, 2017). In this investigation, TMZ was appeared to have cancer prevention agent movement by diminishing serum MDA focuses and expanding both GSH and SOD (Soleymaninejad *et al.*, 2017). Past research has demonstrated that the creation of ROS and the decreased proficiency of the cancer prevention agent guard framework are in charge of the oxidation of lipids, proteins, and different macromolecules, for example, DNA in diabetes. Mammalian spermatozoa have an explicit lipid structure with a high substance of polyunsaturated unsaturated fats, plasma ones, and sphingomyelins (Soleymaninejad *et al.*, 2017). Lipids in spermatozoa are the fundamental substrates of peroxidation and sperm damage using ROS (Civelek *et al.*, 2014). Current examinations demonstrate that hyperglycemic enlistment utilizing alloxan utilized a noteworthy increment in morphologically irregular semen in correlation (Doreswamy *et al.*, 2004). The impact of TMZ was a critical impact of hyperglycemia on morphologically strange sperm. In help of this investigation, hyperglycemia was observed to be high in the clinical setting. Also, other causes of acute hyperglycemia in clinical trials. The study showed that in the diabetic rat induced alloxan, all sperm (Doreswamy *et al.*, 2004 Al-Hajjah *et al.*, 2018). Possible mechanisms of abnormal sperm morphology after oxidative damage may be due to increased damage to DNA due to induction of gene mutations, DNA denaturation, base-pair oxidation, and fragmentation of DNA (El Saghier *et al.*, 2015 Al-Hajjah and Almkhadree, 2018).

CONCLUSION

Tmz has been shown to improve sperm morphology when administered to hyperglycemic rats, which may reflect its antioxidant activity, as previously explained. Thus, in our opinion, TMZ is a good therapeutic option in men with reduced fertility due to prolonged hyperglycemia.

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