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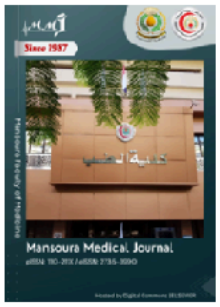

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LIGHT AND ELECTRON MICROSCOPE STUDY OF THE DIABETIC RAT MYOCARDIUM AFTER TRIMETAZIDINE (VASTAREL) TREATMENT

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ABSTRACT

Diabetic patients with ischaemic heart disease have a greater liability of myocardial ischaemia, and an increased incidence of heart failure compared to the non-diabetic ones. The goal of this study was to clarify the effects of trimetazidine on the architecture of the myocardium of diabetic rats. Thirty adult male albino rats (200-250 gm) were used in this investigation. They were divided into three equal groups; control, diabetic non-treated and diabetic TMZ- treated. At sacrifice, small pieces of the myocardium of left ventricle were processed for histological, histochemical and immunohistochemical study. Myocardium of diabetic rats showed an apparent increase of endomysium. The muscle fibers showed areas of degeneration. Ultrastructurally, the cardiac myocytes of diabetic rats showed distortion of cardiac myofibrils with loss of cross banding in many areas. The nucleus had a corrugated nuclear membrane and the mitochondria were swollen and distorted. Histochemically, myocardium of diabetic rats exhibited a weak succinic dehydrogenase reaction and a strong positive immunoreaction for NF-kappa B and caspase-3 in myocardial sarcoplasm. On the other hand, TMZ- treated diabetic rats showed an improvement in the histological architecture and in both histochemical and immunohistochemical reactions. So, TMZ should always be advised for diabetic patients to alleviate the cardiac hazards.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder charatcterized

by widespread complications. Cardiovascular problems have become the major causes of morbidity and mortality in the diabetic population. (Kamal et al., 2005; Marzilli and Affinito, 2005). The long-standing DM can result in the development of cardiomyopathy regardless the coronary artery affection and may be accompanied by myocardial fihrosis (Kerrie et al., 2002; Akula et al., 2003). Several mechanisms are implicated in the pathogenesis of the functional and morphological changes of the myocardium of diabetic patients (Rosano et al., 2005).

Marzilli and Affinito (2005) reported that direct modulation of cardiac metabolic alterations associated with DM appears as a promising choice for the management of ischaemic heart disease. They found that trimetazidine (TMZ) could improve anginal patients without causing haemodynamic changes. El- Kady et al. (2005) and Saeedi et al. (2005) found that TMZ improves post-ischaemic function of pressure overload hypertrophied hearts. This drug intake with the routine treatment up to 18 months is well - tolerated and induces an improvement of the left ventricular function (Di Napoli et al., 2005; O'Meara and McMurray, 2005). Kara et al. (2004) said that TMZ protects the heart against ischaemia-induced arrhythmias and reduces the myocardial infarct size in anaesthetized rats.

A review of the available literature revealed a lack of studies pertaining the histological effects of TMZ on the diabetic myocardium. Consequently, the present investigation was carried out with an intent to throw light on the histological, histochemical and immunohistochemical effects of TMZ on the myocardium of the diabetic albino rats.

MATERIALS AND METHODS

Thirty adult male albino rats (200-250 gm) were used in the present study. They were equally divided into three groups. Group I rats served as control. Group II and III animals were experimental and were given a single dose of streptozotocin (Sigma, St. Louis, MO, USA), 60 mg/ kg i.p., to induce diabetes by specifically damaging pancreatic beta - cells. Successful induction of diabetes was confirmed by elevated blood glucose

levels (more than 300 mg/dl) (Aoki et al., 2001; Evelson et al., 2004). Eight weeks after injection of streptozotocin, group I and II animals were given normal saline (1ml/ day orally for six months). Diabetic animals of group III were given TMZ (Blister of modified release film coated 35 mg-tablets of trimetazidine dihydrochloride manufactured by Servier Egypt Industeries Limited, 6th October City, Egypt, in a dose of 70 mg per day orally, dissolved in 1 ml normal saline). Doses were given orally daily by a modified plastic syringe for six months (Qiu et al., 2005). The human dose of TMZ was corrected according to formula of Paget and Barnes, (1964). All animals were housed under the same conditions and allowed food and water ad-libitum.

Histolgical study :

Twenty-four hours after the last dose of TMZ, rats of all groups were anaesthetized by ether and sacrificed. Small pieces of the myocardium of left ventricle were immersed in 10 % formalin, dehydrated, cleared and embedded in paraffin. Paraffin sections (6 μm) were prepared and stained with haematoxylin & eosin (H&E) to study the general histological architecture of the ventricular myocardium (Drury and Wallington, 1980).

For electron microscopy, fine fragments of the left ventricle were fixed in glutaraldehyde (2%) in 0.1 M phosphate buffer at pH 7.4. They were, then, transferred to 1% osmium tetroxide in the same buffer, dehydrated in ascending grades of alcohol and propylene oxide, embedded in epon (Hayat, 1989). Ultrathin sections (40-50nm) were cut, using a glass knife, stained with 4% uranyl acetate, 2% lead citrate and examined by JEOL 100S electron microscope.

Histochemical study :

Fresh frozen cryocut sections (10μm) were processed for nitro-blue tetrazolium (NBT) staining to estimate the succinic dehydrogenase enzyme (SDH) activity (Kiernan, 1999)

Immunohistochemical study

Paraffin sections of left ventricle (5 μm) were stained by peroxidase anti-peroxidase enzymatic immunohistochemical method(PAP) (Sternbargar et al., 1970), using anti nuclear factor-

kappa B (NF-kappa B, Santa Cruz, USA) (Jones et al., 2003) and anti caspase-3 (Lab Vision, USA) antibodies, invasion system with 3- 3` diaminobenzidine tetrachloride hydrogen peroxidase solution (DAB) as chromogen. The sections were counter stained by Mayer's haematoxylin, dehydrated and mounted (Cai et al., 2002).

RESULTS

Histological changes :

The myocardium of the left ventricle of control rats (group I) showed branching and anastomosing striated muscle fibers separated by a narrow endomysium. They possessed acidophilic cytoplasm and central vesicular nuclei. Flat fibroblasts were noticed at the periphery of the fibers (Fig. 1). The myocardium of diabetic rats (group II) showed an apparent increase in the endomysium between cardiac muscle fibers with numerous fibroblasts. Muscle fibers exhibited areas of degeneration. Some nuclei appeared small and dark (Fig. 2). TMZ-treated diabetic rats (group III) showed a slight increase of the endomysium. Cardiac muscle fibers were more or less similar to the control (Fig. 3).

Ultrastructural changes :

The cardiac myocytes of group I rats exhibited evident cross striations formed by myofibrils. Sarcomeres were bounded by two successive Z lines and showed a dark A band and two halves of light I band. A band showed a lighter H zone in its center, which was bisected by dark M line. The sarcoplasm lodged numerous mitochondria in rows between myofibrils and the nuclei had smooth outlines (Fig. 4). The cardiac myocyte of group II rats showed loss of the normal architecture with focal areas of degeneration. The mitochondria were swollen and distorted. The nuclei possessed corrugated nuclear membranes (Fig.5). An improvement in the histological picture of the cardiac myocyte of group III animals was observed in the form of reappearance of cross banding of sarcomeres. Normal dark bands were bisected by H zone and the light bands appeared very narrow. The nucleus was oval with smooth nuclear membrane. Some myofibrils were still degenerated. The mitochondria were arranged in rows

between myofibrils (Fig.6).

Histochemical changes :

The myocardium of control rats (group I) showed an intense succinic dehydrogenase (SDH) reaction, which appeared as small purple granules scattered in the sarcoplasm of the muscle fibers (Fig. 7). In diabetic rats (group II), the reaction was mostly moderate (Fig. 8). TMZ treated diabetic rats (group III) exhibited an intense reaction in most fibers and a moderate one in some areas (Fig. 9).

Immunohistochemical changes :

1) Nuclear factor kappa B (NF kappa B) : Group I rats showed a weak expression of NF kappa B in the sarcoplasm of cardiac myocytes (Fig. 10). In group II rats, there was a strong positive immune reaction to NF kappa B, which appeared as brownish dots in the cytoplasm (Fig.11). In TMZ-treated diabetic rats (group III), the level of NF-Kappa B reaction in most of cardiac myocytes returned nearly to the control level (Fig.12).

2) Caspase- 3 : Group I rats showed a negative immune reaction to caspase-3 in their myocardial sarcoplasm (Fig. 13). A strong positive immune reaction to caspase-3, was encountered in the cardiac myocytes of group II rats in the form of brownish punctate in the cytoplasm (Fig. 14). Group III animals exhibited a very weak reaction to caspase- 3 in most of their cardiac myocytes and strong reaction in the degenerated ones (Fig.15).

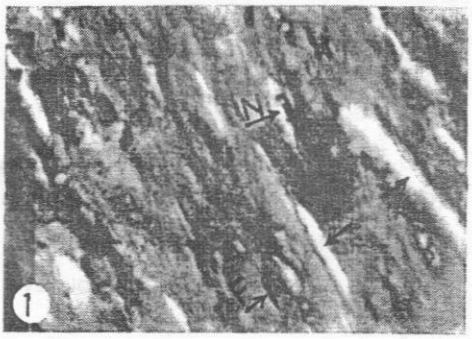

Fig. (1) : A photomicrograph of a control rat (group I) myocardium showing longitudinal striated muscle fibers with central vesicular nuclei (N).Notice the peripheral flat fibroblasts (F) and the narrow endomysium (arrows). (H&E.X400)

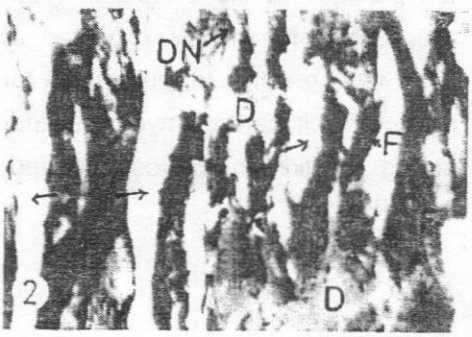

Fig. (2) : A photomicrograph of the myocardium of diabetic rat (group II) showing muscle fibers with areas of degeneration (D). The nuclei are small and dark (DN). Notice the numerous fibroblasts (F) and the apparently increased endomysium (arrows). (H&E.X 400).

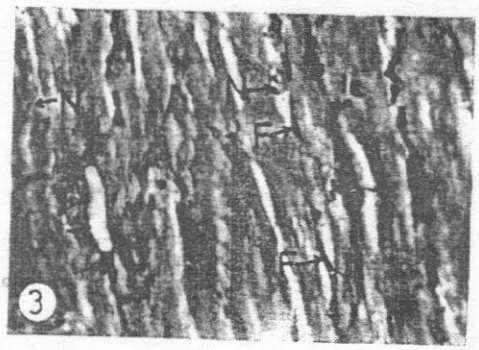

Fig.(3) : A photomicrograph of the myocardium of TMZ- treated diabetic rat (group III) showing a slight increase of endomysium (arrow).Muscle fibers are more or less similar to the control. Notice the vesicular oval nuclei (N) and scattered fibroblasts (F). (H & E. X 400).

Fig.(4) : An electron micrograph of a control rat cardiac myocyte showing cross banding pattern of the myofibrils. Sarcomeres (S) lie between 2 successive Z-lines (Z) and showed dark bands (A) and light bands (I). A band showed a lighter H zone in its center, which was bisected by a dark M line (M). Mitochondria (m) lie between myofibrils in rows. Notice the oval nucleus (N). (Uranyl acetate / lead citrate X 10000).

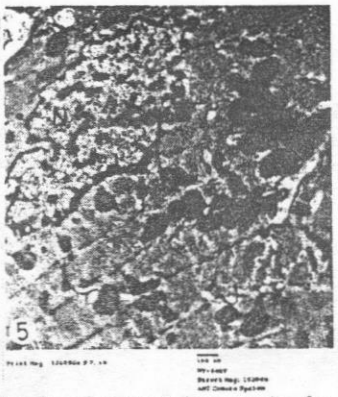

Fig.(5) : An electron micrograph of a cardiac myocyte of group II rat showing distortion of cardiac myofibrils with loss of cross banding in many areas. The nucleus (N) has corrugated nuclear membrane and the mitochondria (M) are swollen and distorted. (Uranyl acetate / lead citrate X 10000).

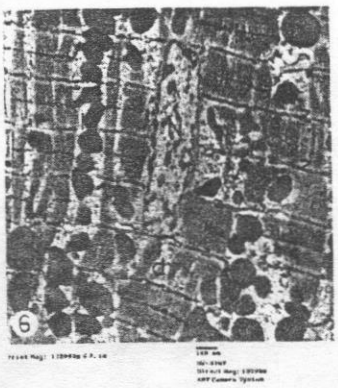

Fig.(6) : An electron micrograph of the cardiac myocyte of group III rat showing regular cross banding of sarcomeres (S).The dark bands are bisected by H zone and the light bands appear very narrow. The nucleus (N) is oval with smooth nuclear membrane. Some myofibrils are still degenerated (d).Notice the mitochondria (M) arranged in rows between myofibrils. Uranyl acetate / lead citrate x10000).

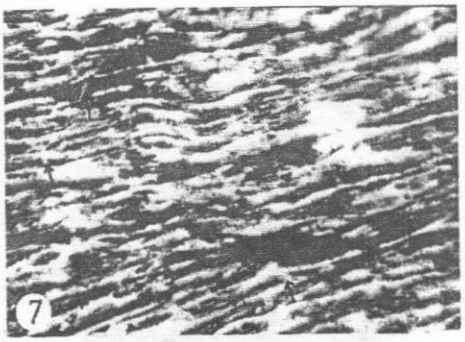

Fig.(7) : A photomicrograph of a control rat myocardium showing intense SDH enzyme activity of muscle fibers with no staining of intercalated disc (arrows). (NBT X 200).

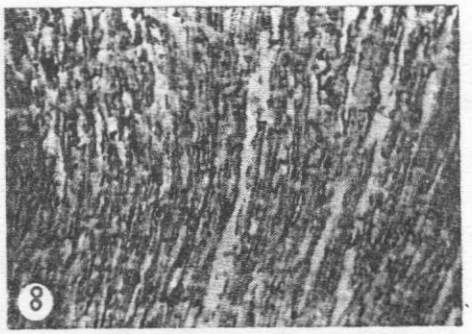

Fig.(8) : A photomicrograph of a diabetic rat myocardium showing mostly a moderate SDH enzyme activity. (NBT X 200).

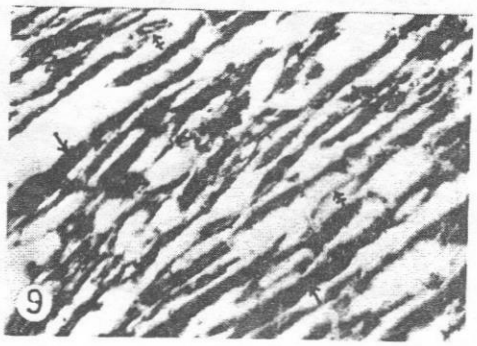

Fig.(9) : A photomicrograph of myocardium of diabetic rat treated with TMZ showing an intense SDH reaction in most fibers (arrows) and moderate reaction in few areas. (crossed arrows). (NBT X 200).

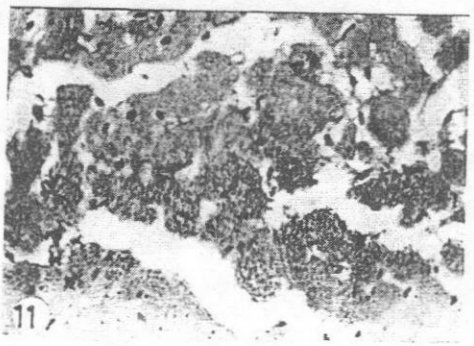

Fig.(11) : A photomicrograph of myocardium diabetic rat showing strong NF-Kappa B reaction in cadriomyocytes. (PAP X 400).

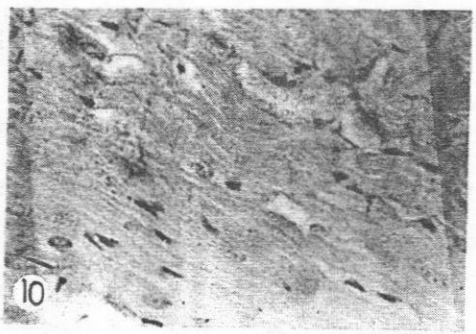

Fig.(10) : A photomicrograph of a control rat myocardium showing weak expression of NF- kappa B in the cytoplasm of myocardium. (PAP x 400).

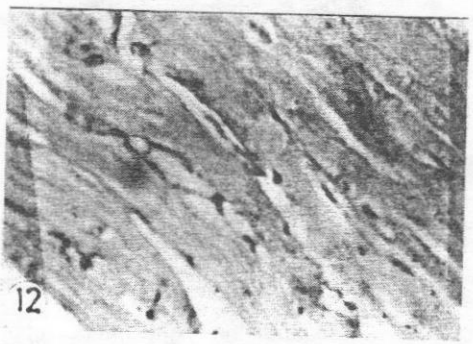

Fig.(12) : A photomicrograph of myocardium of TMZ- treated diabetic rat showing control level of NF-Kappa B reaction in most of cadiomyocytes. (PAP X 400).

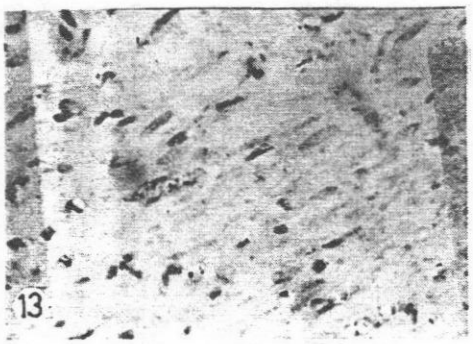

Fig.(13) : A photomicrograph of the control rat myocardium showing negative reaction to caspase-3 in the cytoplasm of cardiac myocytes.
(PAP X 400).

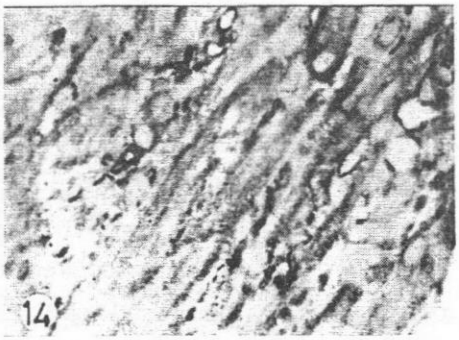

Fig.(14) : A photomicrograph of the myocardium of diabetic rat showing strong reaction to caspase- 3 (PAP X 400).

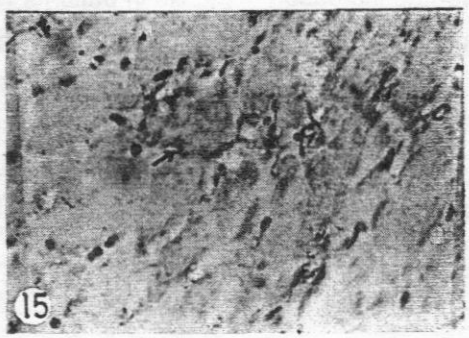

Fig.(15) : A photomicrograph of the myocardium of TMZ- treated diabetic rat showing a very weak reaction to caspase- 3 in the majority of cardiac myocytes with area of strong reaction (arrow) in the degenerated fibers. (PAP X 400).

DISCUSSION

The prevalence of ischaemic heart disease complicating diabetic syndrome is growing rapidly. Management of such a problem remains a challenge; treatments are less effective in diabetic patients than in non diabetic ones. The greater occurrence of ischaemic heart disease is partially due to coronary artery disease and, more importantly, due to the diabetes-induced abnormalities in the myocardium, termed diabetic cardiomyopathy (Marzilli and Affinito, 2005; Stanley, 2005). This cardiomyopathy may be accompanied by myocardial fibrosis (Akula et al., 2003). Rosano et al., (2005) found that the increased uptake and oxidation of free fatty acid by myocardial tissue is responsible for the increased susceptibility of the diabetic heart to myocardial ischaemia compared to the nondiabetic ones.

In the present study, the myocardium of diabetic rats showed an increased endomysium between cardiac muscle fibers with numerous fibroblasts. Muscle fibers showed areas of degeneration. Some nuclei appeared small and dark. These alterations could be due to the diabetic hyperglycaemia and coincides with Thompson et al. (1991), Kerrie et al. (2002) and Adeghate (2004). The wide endomysium, noticed in the present work, could be due to the decreased size of degenerated cardiac muscle fibers. In the current investigation, the myocardium of the TMZ- treated diabetic rats, more or less, regained the control features. This could be due to the effect of TMZ which might combat the hazards of DM on the myocardium. El-Kady et al. (2005) postulated that TMZ improves the ischaemic attacks in patients with ischaemic cardiomyopathy clinically without haemodynamic alterations. Moreover, Parang et al. (2005) claimed that TMZ works by enhancing the efficiency of the myocardium, rather than decreasing its work.

pression of NF-Kappa B was increased. This could be due to the myocardial degeneration by DM. Jones et al. (2003) reported that NF-kappa B is implicated in the regulation of several biological phenomena, including apoptosis, growth, division, immunity and differentiation. Nichols, (2004) added that NF-kappa B is also involved in the cellular responses to stress, hypoxia, stretch and ischemia.

NF-kappa B has been found to be activated by a wide range of stimuli. In unstimulated cells, it is bound to inhibitory molecule in the cytoplasm, which prevents it from entering the nuclei. When cells are stimulated, specific kinases phosphorylate it and cause its rapid degradation and expression in the cell (Jones et al., 2003; Jun et al., 2003). Most of the cardiac myocytes of the TMZ- treated diabetic rats, in this work, regained nearly the control level of NF- Kappa B reaction. This could be due to the beneficial effect of TMZ which counteracts the influences of DM on these cells.

Immunoreactivity for caspase-3 was negative in the cardiac myocytes of the control rats while it was strong positive in the diabetic ones. This could be due to the diabetic stress. This comes in accordance with Feuerstein, (2000) and Venardos et al. (2004) who owed the diabetic alterations to the occurrence of apoptosis in the myocardial cells as a result of mitochondrial changes caused by diabetes. In TMZ- treated diabetic rats, in the current study, immunoreactivity for caspase-3 attained- more or less- the control level. This could be owed to the effect of TMZ on the stressed cardiac myocytes. Green and Reed (1998) showed that mitochondria play an important role in apoptosis under a variety of pro-apoptotic conditions, such as oxidative stress. Also, Roy (2000) and Monteiro et al. (2004) declared that mitochondrial cytochrome C release is a key event in the activation of caspase-3, a pivotal step to initiate apoptosis. TMZ could decrease oxygen free radical production and increase mitochondrial integrity, thus allowing the maintenance of the electrical potential.

In light of the beneficial effects of TMZ in the current investingation, it is

Ultrastructurally, the cardiac myocytes of diabetic rats showed distortion of cardiac myofibrils with loss of cross banding in many areas. The nucleus had corrugated nuclear membrane and the mitochondria were swollen and distorted. These ultrastructural findings could be owed to the stress of diabetic injury and are in agreement with Fitzl et al. (2001) and Searls et al. (2004). Zhang et al. (2002) attributed the diabetic degenerative changes to altered m-RNA expression with impaired protein synthesis and energy production. Devereux et al. (2000) and Srinivasan et al. (2000) emphasized that mitochondrial alterations in diabetic tissues were considered to be one of the characteristic changes. Ghosh et al. (2004) and Stanley, (2005) stated that these alterations could be referred to oxidative stress caused by hyperglycaemia. The cardiac myocytes of TMZ-treated diabetic rats, in this study, showed regular cross banding of sarcomeres with smooth nuclear membrane. Some myofibrils were still degenerated. This apparent improvement in the histological architecture signifies that TMZ could possess cyto-protective effects on the myocardium. This simulated the findings reported by Qiu et al., (2005) who added that TMZ has anti-ischaemic properties without haemodynamic effects.

Diabetic rat cardiac myocytes, in the present work, showed a moderate succinic dehydrogenase (SDH) reaction, which could be owed to altered mitochondria. Similar findings were reported by Velez et al. 1985 who added that SDH is one of the mitochondrial enzymes concerned with energy production and is used as a marker for mitochondrial activity. The cardiac myocytes of diabetic rats treated with TMZ, in the present study, showed an intense SDH reaction in most fibers resembling the control level. This could be due to the beneficial effects of TMZ on the mitochondria. Argaud et al. (2005) claimed that mitochondrial permeability is a pivotal event in cardiomyocyte death following acute ischaemia and TMZ modulates this permeability.

In the current study, NF -kappa B showed a weak expression in the control rat myocardium while in the myocardium of diabetic rats, the ex-

advisable to widen the scale of its use for patients at high risk of diabetes mellitus to alleviate the diabetic undesirable cardiac hazards.

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دراسة بالمجهر الضوئى والإلكترونى لعضلة قلب الفأر المصاب بالسكر بعد علاجها بعقار ترايميتازيدين (فستاريل)

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أجرى هذا البحث لكشف أثر تعاطى عقار ترايميتازيدين (فستاريل) على قلوب الفئران المصابة بمرض السكر. وقد استخدم فى البحث ثلاثون من ذكور الفئران البيضاء البالغة تراوح وزنها بين ٢٠٠ - ٢٥٠جم. قسمت بالتساوى إلى ثلاثة مجموعات.. استخدمت فئران المجموعة الأولى كضابطة وفئران المجموعة الثانية تم إصابتها بمرض السكر وفئران المجموعة الثالثة تم إصابتها بمرض السكر وأعطيت عقار ترايميتازيدين (فستاريل) بعد ثمانية أسابيع من الإصابة بالسكر واستمر العلاج ستة أشهر متتالية عن طريق الفم مرة يومياً.

وقد أظهرت الدراسة الهستولوجية والهستوكيميائية والمناعية الهستوكيميائية التغيرات المصاحبة للاصابة بمرض السكر على عضلة القلب من فقد لترتيب الالياف العضلية مع اتساع فى الغشاء البينى بينها ووجود تحلل فى بعض هذه الألياف. وأصبحت الأنوية صغيرة داكنة وجدارها متعرجاً. وحدث تحلل فى الميتوكوندريا كذلك. ولوحظ أيضاً نقص واضح فى نشاط أنزيم السكسينيك ديهيدروجينيز وزيادة فى التفاعل المناعى للكابا والكسباس-٣. وقد حدث تحسن ملحوظ وغير تام على عضلة القلب بعد اعطاء عقار ترايميتازيدين (فستاريل) ادى الى استعادة الالياف العضلية لمعظم تركيبها الطبيعى كما قلل التفاعل المناعى والكيميائى الدال على تحلل الخلايا.

وبعد استعراض النتائج السابقة يمكن الإستنتاج أن عقار ترايميتازيدين (فستاريل) مفيد لعضلة القلب التى تتأثر بمضاعفا ت مرض السكر.