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Research Article

ROLE OF P53 IN THE ETIOLOGY OF TYPE II DIABETES MELLITUS "APOPTOSISVERSUS CELL-CYCLE ARREST"

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ABSTRACT

In order to estimate the role of p53 in the etiology of type II diabetes, p53 was measured in serum using sandwich ELISA technique in 40 subjects divided into 3-groups according to patient diagnosis and 4-groups with respect to HbA1c%. Serum levels of p53 [U/ml] were higher in type II diabetic patients without complication and type II diabetic patients with proliferative diabetic retinopathy than control subjects. Also, serum levels of p53 were lower in type II diabetic patients with proliferative diabetic retinopathy than diabetic patients without complications. No significant difference appeared between all the studied groups. Also, a statistically non-significant difference was observed in serum levels of p53 in HbA1c% based groups. A statistically significant increase was detected in serum p53 levels when comparing its levels in male with its corresponding levels in female in all studied groups. Alternatively, a statistically non- significant difference appeared in serum p53 levels between groups of the same gender. The results of the current study might reflect a minor role of p53 in the etiology of type II diabetes. Alternatively, it may support the theory of cell-cycle arrest rather than apoptosis.

INTRODUCTION

Type II diabetes mellitus [DM] is a group of metabolic disorders characterized by chronic hyperglycemia and varies from predominant insulin resistance with relative insulin deficiency to a predominant insulin secretory defect with insulin resistance (Kerner & Brückel, 2014; TA, 2014). It manifests itself clinically when the β-cell mass cannot compensate for insulin resistance with insulin release. A great number of studies refer to the reduction in β-cell mass via apoptosis as a contributor to the pathogenesis of type II diabetes(Mandrup-Poulsen, 2001). Alternatively, other studies have found normal β-cell mass (Clark, *et al*., 1988; Kloppel & Drenck, 1983; Rahier, Goebbels, & Henquin, 1983; Stefan, *et al*., 1982; Westermark & Wilander, 1978), so it is still unresolved issue.

Apoptosis is a mechanism of energy-required cellular clearance which may be triggered by several intrinsic and extrinsic factors(Ortega-Camarillo, Flores-Lopez, & Avalos-Rodriguez, 2015). P53 is a major molecule in the apoptotic cascade. P53 network is divided into two main mechanisms, transcription dependent [nuclear activities] and transcription-independent [cytosolic activities](Zilfou & Lowe, 2009). As a transcription factor, p53 transactivates a variety of apoptotic genes including p53 upregulated modulator of apoptosis [PUMA] and Phorbol-12-myristate-13-acetate-induced protein 1 [Noxa](Zilfou & Lowe, 2009). P53 rapid localization to the mitochondria where it governs a group of events ended by cytochrome c release is a part of its transcription-independent mechanism(Green & Kroemer, 2009).

Activation of p53 occurs as a result of DNA damage, oncogene activation, and hypoxia (Zilfou & Lowe, 2009). But the biological outputs differ as it may trigger apoptosis, cell-cycle arrest, senescence, or modulation of autophagy(Green & Kroemer, 2009; Riley, Sontag, Chen, & Levine, 2008; Yee & Vousden, 2005). This variation of p53 functions is attributed to the fact that it acts in a context-dependent manner which is affected by many factors including cell type, the genetic

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background of the cell, the microenvironment of the cell, and the nature of the stress upon the cell(Zilfou & Lowe, 2009). So, the cells respond differentially according to this context-dependent manner.

With respect to pancreatic β-cells, Those responses differ from each other as apoptosis and autophagy result primarily in reduced β-cell mass which secondary progressed to impaired function but cell-cycle arrest and senescence result primarily in impaired function and lately in reduced β-cell mass through holding the mitotic regeneration. Either one of the two hypothesis of reduced β-cell mass or impaired β-cell function has not the ability to exclude the other in the etiology of type II diabetes (Meier & Bonadonna, 2013). Also, the relative role of both defects is still unknown and cannot be estimated.

All of the previous causes enhance the need to achieve the most appropriate mechanism of β-cell failure in type II diabetes in order to get the way to avoid its deleterious complications like diabetic retinopathy [DR] which is a highly specific neuroretinal and microvascular complication of diabetes caused by multiple abnormal metabolic pathways enhanced by uncontrolled hyperglycemia (Saxena, 2016).

This study tries to determine the context-dependent choice of p53 in the pathogenesis of type II diabetic patients with or without diabetic retinopathy.

MATERIALS AND METHOD

Subjects

The study includes 40 subjects. Their ages range between 45 and 60 year, all diabetic patients have controlled blood pressure.

These subjects were basically divided into the following groups after diagnosis via direct and indirect ophthalmoscopy and documented by color photography and fluorescein angiography

Control group: contains 10 healthy subjects. Clinical and laboratory investigations were performed for each to exclude the presence of diabetes mellitus or any associated disease.

Group [1]: contains 15 diabetic patients without complications [DM group].

Group [2]: contains 15 diabetic patients with proliferative diabetic retinopathy [PDR group] which was diagnosed if new vessels were present on the disk or elsewhere on the retina.

Another classification was used in the study based on HbA1c% values includes the following groups

Normal: includes 8 healthy control subjects whose HbA1c% is up to 6%.
Good control: includes 7 diabetic subjects whose HbA1c% ranged from 6.1-7%.

Moderate control: includes 7 diabetic subjects whose HbA1c% ranged from 7.1-8%.

Bad control: includes 16 diabetic subjects whose HbA1c% is over 8%.

Blood Sample Collection and Clinical Investigation

Blood samples were collected; serum was separated and used in quantitative determination of P53 in human serum via enzyme-linked immune-sorbent assay [ELISA] kit purchased from IBL – international GMBH – Germany. Kits for the serum quantitative determination of fasting blood sugar [FBS], Glycosylated HbA1c [%], lipid profile were purchased from Human Gesellschaft for Biochemical and Diagnostic mbH - Germany.

Statistics

Data were collected, checked, revised and entered the computer. Excel computer program was used to tabulate the results. Data analyzed by SPSS statistical package version 24 which was further used was to represent it graphically. One Way ANOVA was used to declare the significant difference between groups at $p<0.05$. Duncan multiple comparisons test at $p<0.05$ was used to declare the significant difference between each two groups. Pearson's correlation coefficient was used to declare the significant correlation between the quantitative parameters within each group at $p<0.05$. One Way ANOVA was also used to declare the significant difference in serum p53 concentration [U/ml] in groups based on HbA1c% values at $p<0.05$.Tukey test at $p<0.05$ was used to declare the significant difference between each two groups. Two Way ANOVA was used to declare the significant difference between male and female in each group at $p<0.05$.

RESULTS

As regards, a statistically non-significant increase in serum p53 was detected when comparing its values in DM group and PDR group with its corresponding values in control group. Also, a statistically non-significant increase in serum p53 concentrations was seen on comparing DM group with PDR group.

A statistically significant increase in age of patients [year] was observed in both DM group and PDR group compared to healthy controls with a non-significant difference in age of patients between DM group and PDR group. Also, a statistically significant increase in duration of diabetes [year] among PDR group was observed compared to DM group.

On the other hand, a statistically-significant increase in FBS [mmol/l] was detected when comparing its values in DM group and PDR group with its corresponding values in control group. This significant increase was highly represented in PDR group when compared to DM group.As a comment on the results of HbA1c [%], a statistical-significant increase in its percentage in DM group and PDR group was observed compared to control group. But this increase did not reach to a level to be significant in PDR group compared to DM group.

With respect to serum total cholesterol [mmol/L] and serum LDL-cholesterol [mmol/L], a statistical-significant increase was observed in comparing DM group and PDR group with control group. Otherwise, a non-statistical significant decrease was observed in comparing PDR group with DM group. Those findings are parallel to a statistical-significant decrease detected in comparing serum HDL-cholesterol [mmol/L] in DM group and PDR group with control group added to a statistical non-significant difference observed between DM

group and PDR group. Also, a statistical-significant increase in serum triglycerides [mmol/L] was observed in comparing both DM group and PDR group with control group beside a non-significant increase detected in PDR group compared to DM group. No correlations are seen between serum p53 levels and clinical indicators of diabetes, age, duration of diabetes, and lipid profile.

Upon applying HbA1c% based groups, a statistically non-significant increase in serum p53 values was observed in good control group compared to normal group. Furthermore, a statistically non-significant decrease in serum p53 values was detected in moderate and bad control groups compared to good control group beside a non-significant decrease in serum p53 values in bad control group compared to both moderate control and normal groups. Also, a statistically non-significant increase in serum p53 values was observed when comparing moderate control group with normal group.

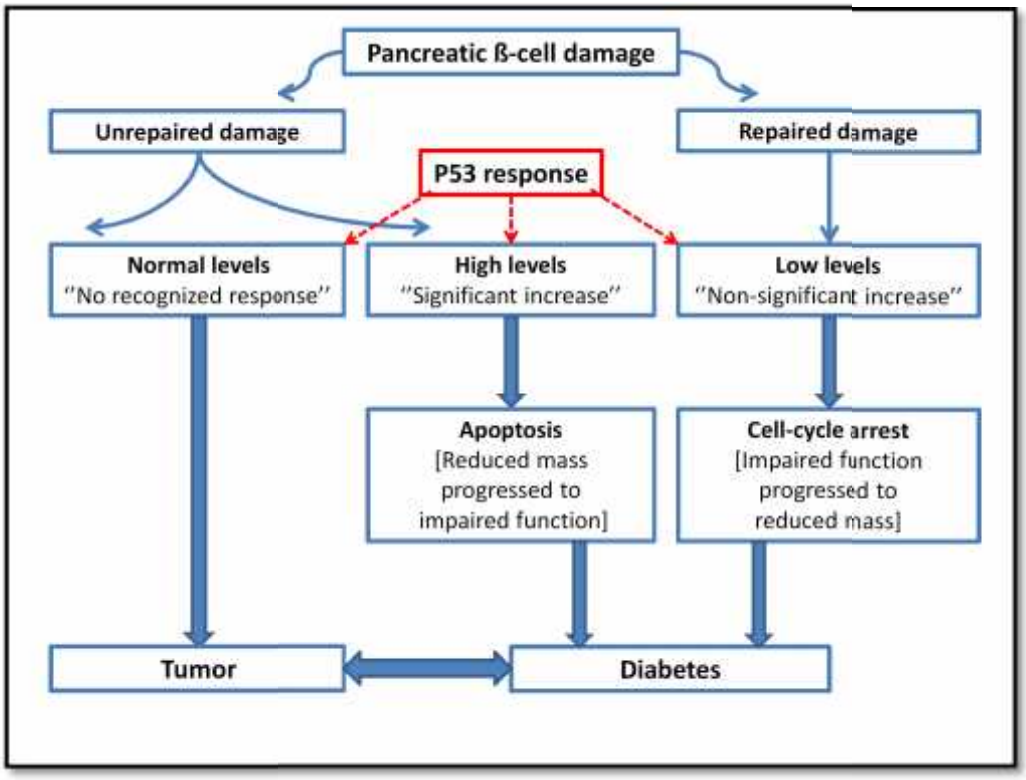

Figure 1 Proposed p53 response to varies types of damages in pancreatic β-cells
The diagram suggested that the etiology of diabetes is dependent on the type of damage and the magnitude of p53 response. Also, it stated that apoptosis might represent the alternative choice of tumor in case of irreversible unrepaired damage.

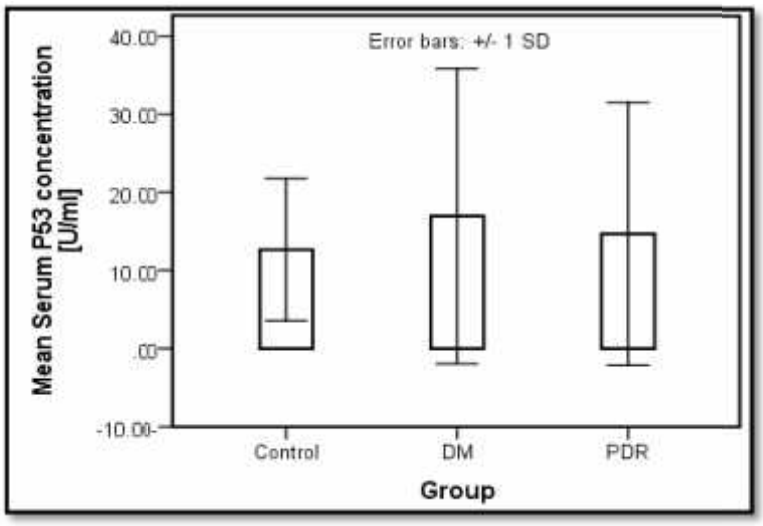

Figure 2 Levels of p53 concentration 'U/ml' in all studied groups

A statistically non-significant increase is detected in serum p53 concentration 'U/ml' when comparing its values in DM group and PDR group with its corresponding values in control group. Also, a non-significant increase in serum p53 concentrations was seen on comparing DM group with PDR group.

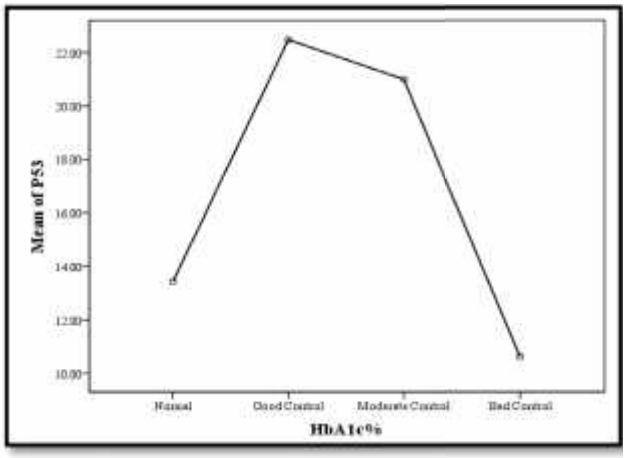

Figure 3: Levels of p53 concentration 'U/ml' in HbA1c%-based groups
Non-significant difference was observed in serum p53 Concentrations 'U/ml' in groups based on HbA1c%. Non-significant increase in serum p53 values was detected in good control group compared to normal group. Non-significant decrease in serum p53 concentration 'U/ml' was observed in moderate and bad control groups compared to good control group. Non-significant decrease in serum p53 concentration 'U/ml' was detected in bad control group compared to both moderate control and normal groups. Also, non-significant increase in serum p53 concentration 'U/ml' was observed when comparing moderate control group with normal group.

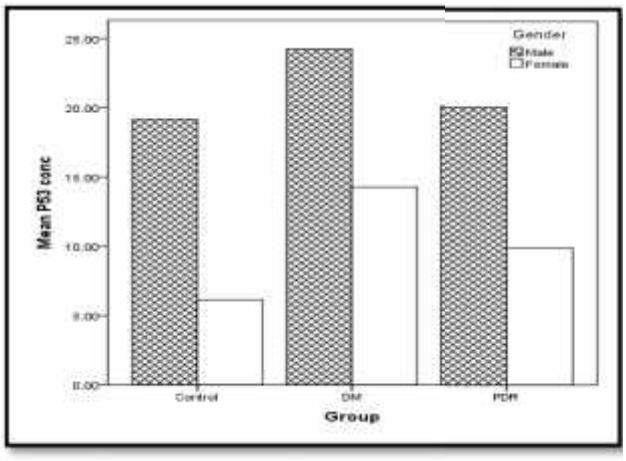

Figure 4: Effect of gender on levels of p53 concentration
A statistically significant increase was detected in serum p53 concentration 'U/ml' when comparing its values in male with its corresponding values in female in all studied groups. Alternatively, no significant difference appeared in p53 levels between groups of the same gender.

Taking gender into consideration, a statistically significant increase was detected in serum p53 when comparing its values in male with its corresponding values in female in all studied groups. Alternatively, a statistically non- significant difference appeared in p53 values between groups of the same gender.

Table2: Serum p53 group differences based on gender
Data are mean ± standard deviation [SD] deduced from SPSS statistical package version 24 via using Two-Way ANOVA test**.**

Groups	Mean ± SD	
	Male	Female
Control	$19.15^{a} \pm 8.15$	$6.15^{b} \pm 3.84$
DM	$24.25^{a} \pm 17.63$	$14.28^{b} \pm 19.45$
PDR	$20.11^{a} \pm 22.59$	$9.90^{b} \pm 8.53$

Different letters means that there is a significant difference

DISCUSSION

It has been shown in multiple other studies that apoptosis of pancreatic β-cells has a major role in the pathogenesis of type II diabetes and its very dangerous complication diabetic retinopathy [DR] (Allen, Yaqoob, & Harwood, 2005; Butler, *et al*., 2003).

The non-significant difference in serum p53 observed in both diagnosis-based groups and HbA1c%-based groups doesn't fulfill the enough evidence to ensure the role of p53 in the pathogenesis of DM or the progression of its complications. These results do not deny the participating of β-cell apoptosis in the pathogenesis of DM or its complications as it may proceed via another cell-death mechanisms which do not involve p53. So, these apoptotic mechanisms affect the number of pancreatic β-cells in a continuous reduction manner which result in reduction of serum p53 values of PDR group in comparison with DM group. This finding became strong by the study of Nam, S. Y., *et al* [2008] (Nam, Lee, & Sabapathy, 2008) which stated that the tumor-suppressor p53 is not required for pancreatic β-cell death during diabetes and upon irradiation. Also, Clara O. Camarillo *et al* [2015] study (Ortega-Camarillo, *et al*., 2015) presented evidence that hyperglycemia increases the percentage of time-dependent apoptosis without changes in p53 expression.

Table 1: Serum p53 and clinical characteristics of the studied groups
Data are mean ± standard deviation [SD] deduced from SPSS statistical package version 24 via using Analysis of Variance [One-Way ANOVA] testand Duncan multiple comparisons testat p<0.05.

Parameters	Mean ± SD		
	Control n=10	DM n=15	PDR n=15
Serum P53 Concentration [U/ml]*	$12.64^{a} \pm 9.11$	$16.93^{a} \pm 18.91$	$14.66^{a} \pm 16.82$
Age of Individuals [year]**	$39.70^{a} \pm 6.32$	$54.73^{b} \pm 9.42$	$55.13^{b} \pm 10.74$
Duration of Diabetes [year]**	-	$8.10^{a} \pm 5.05$	$13.73^{b} \pm 6.37$
Fasting Blood Sugar [mmol/L]**	$5.03^{a} \pm 0.56$	$8.19^{b} \pm 1.51$	$11.04^{c} \pm 3.11$
Glycosylated HbA1c [%]**	$4.72^{a} \pm 1.01$	$8.68^{b} \pm 1.95$	$9.02^{b} \pm 2.06$
Serum Total Cholesterol [mmol/L]**	$4.51^{a} \pm 0.86$	$5.58^{b} \pm 0.65$	$5.36^{b} \pm 1.23$
Serum HDL-Cholesterol [mmol/L]**	$1.41^{b} \pm 0.29$	$1.01^{a} \pm 0.16$	$1.02^{a} \pm 0.31$
Serum LDL-Cholesterol [mmol/L]**	$2.73^{a} \pm 0.98$	$4.05^{b} \pm 0.44$	$3.69^{b} \pm 0.84$
Serum Triglycerides [mmol/L]**	$1.00^{a} \pm 0.54$	$1.67^{b} \pm 0.47$	$1.89^{b} \pm 0.64$

* Insignificant difference P>0.05
** Significant difference P<0.05
# Different letters means that there is a significant difference between the two groups

Within the intrinsic apoptotic pathway, p53 acts as a manager regulator of the expression of both anti-apoptotic proteins and pro-apoptotic proteins (Elmore, 2007). So, it dominates on mitochondrial initiated apoptotic events (Elmore, 2007). The results of this study meantneglected or at least minor role of the intrinsic apoptotic pathway [mitochondrial pathway] which is p53-dependent.

Also, it pointed to the limited participation of the intrinsic apoptotic signaling materials like cytochrome c whose levels do not differ between diabetic patients without complications and diabetic patients with complications as elucidated before (Dincer, *et al*., 2009). So, it is not good to use any of the intrinsic apoptotic signaling materials as p53 or cytochrome c to test the pancreatic β-cell behavior during DM and its complications (Dincer, *et al*., 2009). But p53 may aid in the prognosis and early diagnosis of type II DM (Dincer, *et al*., 2009).

Two possible apoptotic pathways are p53-independent processes. They are called extrinsic pathway [death receptor pathway] and perforin/granzyme pathway.

The evident increase in inflammatory cytokines as TNF-α accompanying DM onset and progression provides the ligands for the extrinsic apoptotic pathway (Ryan, Murphy, Godson, & Hickey, 2009). This pathway involves the transmission of the death signal from outside to inside the cell. Fas L/Fas R and TNF-α/TNF-R1 models represent good examples for the study of the extrinsic apoptotic pathway (Elmore, 2007). Upon extracellular ligand-receptor binding, an intracellular death domain also binds to the receptor such as Fas-associated death domain [FADD] and TNF-receptor associated death domain [TRADD] (Elmore, 2007; Hsu, Xiong, & Goeddel, 1995; Wajant, 2002). The death-effector domain together with procaspase-8 forms a death-inducing signaling complex [DISC] that activates caspase-8(Elmore, 2007; Kischkel, *et al*., 1995). Finally, it pours into the execution pathway through caspase-3 activation (Elmore, 2007). Caspase-3, as the most important executioner caspases including caspase-6 and caspase-7, begins a cascade of events yielding the morphological and biochemical features of the apoptotic cells (Elmore, 2007; Slee, Adrain, & Martin, 2001).

The other pathway called perforin/granzyme pathway also represents an inflammatory response via accumulation and activation of cytotoxic T-lymphocytes [CTLs]. It involves the secretion of the transmembrane pore-forming molecule perforin by CTLs followed by exophytic release of cytoplasmic granules through the pore and into the pancreatic β-cells (Trapani & Smyth, 2002). Granzyme A and granzyme B are the most important components within the granules (Elmore, 2007). Granzyme B acts in a caspase-dependent manner via activation of caspase-3 (Barry & Bleackley, 2002; Russell & Ley, 2002). Alternatively, granzyme A acts in a caspase-independent manner through cleavage of the nucleosome assembly protein [SET] that protects the chromatin and DNA structure. So, it provides a chance to the tumor suppressor gene product DNAse NM23-H1 to evoke apoptosis (Elmore, 2007). But the approximately constant cytochrome c released in diabetic patients with and without complications (Dincer, *et al*., 2009) threatens the probability of perforin-granzyme pathway because granzyme A enhance the mitochondrial pathway through cleavage of BH3 Interacting Domain Death Agonist [Bid] and induction of cytochrome c release (Barry & Bleackley, 2002; Russell & Ley, 2002).

So, it is obvious that the most appropriate apoptotic mechanism is the extrinsic pathway [death receptor pathway]. This mechanism continuously affects the number of pancreatic β-cells as the rate of apoptosis declines over time in proportional with the rest of cells. This means that the maximum rate of apoptosis is at the onset of the disease then it declines periodically. This point of view can provide an explanation for the reduction of serum p53 values in PDR group compared with DM group in response to the reduction in the number of pancreatic β-cells.

Alternatively, the fact that the difference in serum p53 in all studied groups did not reach significant values could not be ignored. So, another possible mechanism is highlighted which is dependent on the participation of p53 in cell-cycle arrest. This point of view reveals that the malfunctioning of pancreatic β-cells begins with loss of function due to cell-cycle arrest and further progresses to loss of mass due to impaired regeneration. This may demonstrate the antagonism and competition between several research results. Earlier reports about the reduction of β-cell mass in type II diabetes were ambiguous as it might have included cases of type I diabetes. However, recent reports with a well characterized clinical data concluded that β-cell mass is decreased in type II diabetes, whereas, others report no decrease in β-cell mass (Butler, *et al*., 2003).

It is better to note that this research did not deny the role of apoptosis in the pathogenesis of DM as gained by different studies. However, it added the possibility of cell-cycle arrest in case of reversible damage. Also, it attributed the data supporting the apoptotic theory to the irreversible damages where it is obligatory to perform apoptosis instead of tumorgenesis. It is important to mention that the results of all of the previous agreed with or opposed to the apoptosis theory plus the current study are population-dependent.

Knowing that the role of p53 in cell-cycle arrest has been ensured through different experimental studies,the theory of cell-cycle arrest may displace that of apoptosis. Quantitative changes to p53 directly impact its biological output according to p53 first model context-dependent and as previously shown by experiment that low levels of p53 can lead to cell-cycle arrest, whereas increasing levels can trigger apoptosis (Zilfou & Lowe, 2009).

Also, cell-cycle arrest might explain the finding of both Laedtke, T., *et al* [2000] and Weng, J., *et al* [2008] (Laedtke, *et al*., 2000; Weng, *et al*., 2008)who stated that an early improvement or recovery of some cases after insulin therapy occurred because the administration of insulin decreased stress upon β-cells and provided the enough needed time for pancreatic β-cells to get rid of its arrest. This fast reversibility is considered as an evidence for function related not mass related β-cell failure and by the way cell-cycle arrest hypothesis. But this improvement did not extend as a progressive draw back in β-cell function was developed over time (Meier & Bonadonna, 2013) may be due to lately impaired regeneration after cell-cycle arrest.

Further accumulated evidence for cell-cycle arrest hypothesis came from the study of the percentage of reduction of β-cell mass required to develop type II diabetes in different species. It had been shown that the onset of DM is strongly correlated with β-cells regeneration capacity rather than apoptosis. In several animal models, 50% of β-cell reduction is enough to produce type II diabetes, but in human about 65% reduction in β-cell develops type II diabetes. Mice and rats are excluded due to their unique capacity of β-cell regeneration especially in young rodents as they could maintain glucose homeostasis up to 60-90% β-cell loss (Bonner-Weir, Trent, & Weir, 1983; Goodner, Koerker, Weigle, & McCulloch, 1989; Meier, Kjems, Veldhuis, Lefèbvre, & Butler, 2006). The regeneration capacity provided to those small young animals is not extended to large animals and human (Meier & Bonadonna, 2013). So, the capacity of β-cell regeneration depends on race and age.

The results of the current study support the impaired regeneration of the pancreatic β-cell through cell-cycle arrest which holds the mitotic division and adaptation to the increased insulin demand. This may be better explained by impaired β-cell regeneration parallel to normal apoptotic rate. Also, cell-cycle arrest is suitable to resolve the competition between reduced β-cell mass and impaired β-cell function in the pathogenesis of type II diabetes via the concept of reduced functional β-cell mass at the onset. This means that the number of β-cells that perform its function is decreased after cell-cycle arrest without change in the overall mass. But, the mass is lately affected by time due to impaired mitosis and further regeneration.

In spite of the previously mentioned reasoning that supported the hypothesis of cell-cycle arrest against apoptotic theory, it was not sufficient to entirely deny the later.

CONCLUSIONS

The current study added another phenomenon as it stated that pancreatic β-cells cell-cycle arrest may replace apoptosis in the etiology of type II diabetes and further its complications. Finally, the research outputs give hope to humanity to recover from DM and encourage the researchers to get a suitable therapy to restore pancreatic β-cells from cell-cycle arrest and further to maintain their functional capacity. Searching for a way to determine and repair the reversible damage resulting in cell-cycle arrest is a must for the novel therapeutic approaches. Also, it may be harmful for the cell to reverse the apoptotic mechanism if it is found in case of irreversible harmful damage. So, the need for personal therapy based on genetic mapping is growing over time.

Further studies are recommended to illustrate the effect of different types of damage on pancreatic β-cells to differentiate between mutations resulting in either β-cell apoptosis or cell-cycle arrest.

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