

## Selenium Controlled Diabetic Cardiomyopathy Complications

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### ABSTRACT

Secondary complications of diabetes develop gradually in longer terms. The longer you have diabetes the higher the risk and severity of the complications. Sooner or later, diabetes induced complications may result in the paucity of the physiological functions of the body which in turn give rise to life-threatening situations. Although we need small quantities still selenium plays a key role in the body metabolism. Indeed, having an antioxidant characteristic, it protects many cell types from damage especially during chronic diseases.

**Keywords:** Physiological functions; antioxidant; metabolic disorder.

### INTRODUCTION

Diabetes mellitus is a metabolic disorder caused either by the deficiency in the production of insulin (type 1), or by the ineffectiveness of it (type 2). Presence of the different entities of diabetes was first stated by Sir Harold Percival Himsworth in 1936. In any of these entities uncontrolled blood glucose is a common end point, which in turn affects the vital functions of the body's systems.

Secondary complications of diabetes develop gradually in longer terms. The longer you have diabetes the higher the risk and severity of the complications. Sooner or later, diabetes induced complications may result in the paucity of the physiological functions of the body which in turn give rise to life-threatening situations. Among many other complications cardiomyopathy, neuropathy, nephropathy and retinopathy are the most principal ones that increase patient's morbidity and mortality.

The biological systems are continuously exposed to oxidants which are generated either by deliberately or as byproducts. These oxidants are able to initiate many enzyme- and gene-dependent reactions in both physiological and pathophysiological conditions. Having paramagnetic free radicals these oxidants can be classified as reactive oxygen species (ROS) and reactive nitrogen species (RNS). Indeed, deficiencies or overproduction of ROS and/or RNS can result in pathological state through impaired homeostasis.

Selenium –trace element from soil-naturally appears in water and some foods. Although we need small quantities still it plays a key role in the body metabolism. Indeed, having an antioxidant characteristic, it protects many cell types from damage especially during chronic diseases.

This review covers current knowledge of the role of selenium in the diabetic cardiomyopathy. We

describe, in depth, selenium as an antioxidant either protects or restores the diabetes induced electrical remodeling of the heart tissue.

### Diabetic Cardiomyopathy

Diabetic cardiomyopathy is the latest complications of diabetes - is one of the most fundamental causes of diabetes induced deaths and poor quality of life<sup>1</sup>. Type independently; it is characterized by the dysfunctions in the early-onset diastolic and the late-onset systolic periods.<sup>2</sup> In experimental models studies of diabetes, this type of cardiomyopathy is characterized by the mechanical, biochemical and morphological abnormalities in the heart tissue.<sup>1</sup> Although the disease at first characterized by the left ventricular expansion and restrained of systolic function but later the diastolic left ventricular dysfunction was also identified.<sup>3,4</sup>

In longer terms of diabetes, significant changes in the heart tissue such as impaired lipid metabolism and increase in oxidative stress causes an electrical remodeling. As a result of these changes have been observed that in AP and contraction period are dysfunctions as a consequence of ionic current impairments.<sup>1,5,6</sup> These implies the relationship between the action potential and muscle contraction parameters which known as excitation contraction coupling. It is well known fact that the excitation and contraction processes are strictly connected especially for the heart tissue i.e alteration in one concomitantly affects the other.

### Abnormalities in Contraction Parameters

Diabetic cardiomyopathy includes alterations in intracellular free  $Ca^{2+}$  ( $[Ca^{2+}]_i$ ) homeostasis which in turn leads to contractile malfunctions.<sup>7</sup> Researches dealing with the left ventricular papillary muscles isolated from streptozotocine (STZ)-induced diabetic rats and rabbits have shown that the prolonged contraction and relaxation periods<sup>5,8</sup> associated with the down regulation of  $Ca^{2+}$  uptake by the sarcoplasmic reticulum (SR).<sup>9</sup> In accordance with the uptake results of fluorometric ( $[Ca^{2+}]_i$ ) measurements of showed a prolongation in the contraction and relaxation periods of diabetic myocytes<sup>10,11</sup>. These effects which occur in the sarcoplasmic reticulum are mostly attributed to the reduction in the amount of ryanodine receptor protein (RyR2), SR  $Ca^{2+}$ -ATPase

protein content, and SR  $Ca^{2+}$  storage capacity. However, L-type  $Ca^{2+}$  currents ( $I_{CaL}$ ) and channel protein content remained same<sup>9,10,12</sup>. Fauconnier *J et al.* has been reported that  $I_{to}$  decreases as a consequence of increased diastolic calcium content following RyR2 changes, which it explains that diabetes exhibits some similarities with heart failure.<sup>12</sup>

These changes in the contraction parameters as a consequence of cardiomyopathy are summarized on the table 1.

### Abnormalities in AP Parameters








Fein *et al.* (1980), for the first time, demonstrated the effects of diabetes mellitus on the duration of action potential and ionic currents with experimental diabetic animal model studies.<sup>1</sup> In his pioneer work, it was reported that the diabetes results in an increase in the action potential (AP) duration and a decrease in ventricular AP amplitude.<sup>1</sup> Researches focused on the underlying mechanism of this prolonged repolarization phase of the AP ended up with the down regulated potassium currents. Indeed, deep patch clamped studies have shown that there was a tremendous decrease in transient outward potassium current ( $I_{to}$ ) and steady state outward  $K^+$  current ( $I_{ss}$ ) but invert rectifier ( $I_{Kr}$ ) on the other hand remained same.<sup>6</sup> Furthermore, it is well known that the prolongation in AP duration is due to by not only the inhibition of  $K^+$  currents but also the reduction of  $Na^+ - Ca^{2+}$  exchanger current.<sup>13</sup> Taken together, the present data indicate that  $[Na^+]_i$  is an important modulator of excitation-contraction coupling by regulating  $Ca^{2+}$  efflux / influx. Bilginoglu *et al.* have shown that the less  $Na^+$  influx during contraction in diabetic rat heart tissue reduces  $Ca^{2+}$  influx in diabetic cardiomyopathy.<sup>14</sup>

These changes in the action potential parameters as a consequence of diabetic cardiomyopathy are summarized on the table 2.

### Oxidative Stress

The effective usage of input is a very significant step in evolution. Thus oxidative phosphorylation has the greatest importance due to its high energy yield. It is a series of oxidation-redox reactions in which the molecular oxygen is

Table 1: Contraction parameters.






Duration of Contraction and Relaxation	Relaxation and Contraction Rate	RyR2 Amount	SR Ca <sup>2+</sup> Storage by SR	SR Ca <sup>2+</sup> -ATPase	I <sub>CaL</sub>	Uptake of Ca <sup>2+</sup>	[Ca <sup>2+</sup> ] <sub>i</sub>
Prolongation <sup>8,5</sup>	Slow <sup>8,5</sup>	Decrease <sup>12</sup>	Decrease <sup>12</sup>	Decrease <sup>12</sup>	No change <sup>5</sup>	Decrease <sup>5</sup>	Increase <sup>11</sup>
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an electron donor but the reaction has reactive intermediates. The oxidation is the major drawback since it is called as one of the main causal in many disorders including diabetes mellitus.

In an atomic order of magnitude, oxidation can be explained as an increase in electron spin resonance, which is a result of unpaired electrons. By using the definition of the “nearsightedness of electrons” in many atomic systems, it is easier to visualize the effects of the oxidation. The definition posits that in the absence of the long-range ionic interaction large molecules can be studied one neighborhood at a time, so it is not necessary to study the whole system at once<sup>15</sup>. In this point of view, the effect of a reactive molecule in the entire system -in the body- can be ignored easily, but the local effect on the other hand can be as destructive as a category 4 hurricane.

The fine tuned balance in the oxidative system (oxidant and antioxidant) is essential for sustaining life properly. If the balance shifts in the favor of the former the oxidative stress occurs, that leads a potential damage in its vicinity<sup>16</sup>. Since oxidation, the production of the reactive oxygen species such as superoxide and hydrogen peroxide, is inevitable, it is wise to find ways to reinforce the endogenous antioxidant defense mechanisms in the body by adding antioxidant supplements to the daily diets, which helps to scavenge free radicals. In the light of the animal model studies, a wide variety of substances are recommended as supplements - spans from tungsten<sup>17</sup>, a transition metal, to resveratrol<sup>18,19</sup>, vitamin E<sup>20</sup>, curcumin<sup>21</sup>, and selenium- that<sup>22</sup>, have positive effects on the diabetes mellitus related complications. Among the others, selenium needs more attention because selenium, an essential trace element, functions as a cofactor for glutathione peroxidases and a key parameter in selenoproteins such as thioredoxin reductase<sup>23</sup>.

Table 2: Action potential parameters

AP Duration	AP Amplitude	I <sub>K1</sub>	I <sub>to</sub>	I <sub>ss</sub>
Prolongation <sup>1</sup>	Decrease <sup>1</sup>	No change <sup>6</sup>	Decrease <sup>6</sup>	Decrease <sup>6</sup>
				

### Selenium intake and Diabetes

Diabetic milieu, the main reason of the diabetic cardiomyopathy, alters protein kinase C, causes abnormalities in lipid metabolism, action potential duration, calcium ion homeostasis, and antioxidant defense, which causes an electrical remodeling in the heart<sup>24</sup>. The electrical remodeling in diabetes is well known and the electrophysiological studies reveal the underlying ionic mechanism. It is known that potassium ion channels are responsible not only for the repolarization of the action potential but also for maintaining the resting membrane potential in the heart. The modulation of the potassium channels are the primarily reason of the electrical remodeling of cardiac action potential<sup>25</sup>. Thus, one must restore the alteration in the potassium ion channels to cure or decelerate the complications of diabetic cardiomyopathy. The reason of downregulation in potassium currents is not well known yet, but it is found that oxidative stress and hyperglycemia are involved in this remodeling<sup>26</sup>. The studies about glutathione have promising results on potassium channels. The oxidative stress results in a decrease in reduced glutathione (GSH) and an increase in oxidized glutathione (GSSG). The accumulation of GSSG results the oxidation of protein thiol groups of cysteine residues.

Moreover, it is stated that along with its antioxidant property insulin like characteristics brings selenium one more step further. The main issue in diabetes mellitus is the impairment in glucose transport mechanisms; selenium, like insulin, translocates the glucose transporters on the cell membrane. Furthermore, it stimulates the activity of CAMP phosphodiesterase, and phosphorylation of ribosomal S6 protein. Since, in the absence of insulin, selenium failed to stimulate insulin receptor kinase activity it is probable that effect of the selenium is on other tyrosine kinase. Interestingly, in the presence of insulin, selenium enhances insulin receptor kinase activity and phosphorylations of insulin-stimulated tyrosylphosphoproteins<sup>27</sup>.

It is well known that calcium is the most important ion in regulating contraction in the heart. Diabetic milieu and oxidative stress also affect contracting channel proteins and causes hyperphosphorylation of PyR2 which causes a leakage from SR<sup>28</sup>, moreover the abnormalities

in Ca<sup>2+</sup> transients<sup>29</sup>, and an increase in basal intracellular calcium concentration is observed<sup>30</sup>. The selenium application has restored the observed abnormalities<sup>31</sup>, but since the selenium effects in a dose dependent manner, the reverse –no significantly alter the contraction related parameters– is also proposed in some studies<sup>26,32</sup>.

Since the effects of selenium supplementation can be seen in metabolism through various pathways, in the literature the different effects of it are reported. It is stated that the combination of insulin and selenium suppresses the cardiomyocyte apoptosis through inhibiting the p38MAPK/CBP pathway<sup>33</sup>. Furthermore, selenium restores depressed Beta-adrenergic responses of the heart in diabetic rats<sup>34</sup>. Besides its antioxidant and hypolipidemic effects<sup>35</sup>, due to its anti-inflammatory activity, it has a beneficial effect on the regulation of the leukotriene pathway in diabetic cardiac hypertrophy heart<sup>36</sup>. Not only diabetes mellitus but also cardiovascular diseases are also linked to low plasma selenium levels<sup>37</sup>. It is reported that supplementation is beneficial in patients with type 2 diabetes and coronary heart disease and significantly reduces the mortality<sup>38,39</sup>, and it protects the heart against ischemia/reperfusion (I/R) injury due to its action on cellular redox state and deactivation of NF- $\kappa$ B in I/R hearts<sup>40</sup>.

Recent and promising results are from the studies on the selenium nanoparticles. It is stated that insulin loaded selenium nanoparticles may overcome the oral insulin delivery problem and increase the comfort of the patients. Insulin loaded selenium nanoparticles could alleviate oxidative stress, improve pancreatic islet function, and promote glucose utilization<sup>41</sup>. By same token, elemental selenium nanoparticles delivered in liposomes has higher absorption than dietary selenium which may be explained by different absorption mechanisms and metabolic pathways<sup>42</sup>. The promising results of selenium studies conclude that it is wise to include selenium in treatment approaches for diabetes.

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## REFERENCES

1. Fein, F, Kornstein L, Strobeck J. and Sonnenblick E. Altered myocardial mechanics in diabetic rats. *Circulation Research*, **47**: 922–933 (1980).
2. Poornima, I.G, Parikh P. and Shanno R.P. Diabetic cardiomyopathy: The search for a unifying hypothesis. *Circulation Research*, **98**(5): 596–605 (2006).
3. Karamitsos, T. D, Karvounis H. I, Dalamanga E. G, Papadopoulos C. E, Didangellos T. P. and Karamitsos D. T. Early diastolic impairment of diabetic heart: The significance of right ventricle. *International Journal of Cardiology*, **114**(2): 218–223 (2007).
4. Zarich, S.W, Arbuckle B.E, Cohen L.R., Roberts M. and Nesto R.W. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. *Journal of the American College of Cardiology*, **12**(1): 114–120 (1988).
5. Fein, B, Miller-Green B, Zola H. and Sonnenblick A.M. *J.Physiol. Heart Circ. Physiol*, **250**: H108–H113 (1986).
6. Shimoni, Y, Firek L, Severson D. and Giles W. Short-term diabetes alters K<sup>+</sup> currents in rat ventricular myocytes. *Circ Res.*, **74**(4): 620-8 (1994).
7. Vassort G. and Turan B. Protective Role of Antioxidants in Diabetes-Induced Cardiac Dysfunction. *Cardiovasc Toxicol*, **10**:73–86 (2010). DOI 10.1007/s12012-010-9064-0.
8. Fein, L.B, Kornstein J.E, Strobeck, J.M, Capasso E.H. and Sonnenblick. *Circ. Res.*, **15**: 922–933 (1980).
9. Ganguly, P.K, Pierce G.N, Dhalla K.S. and Dhalla N.S. Defective sarcoplasmic reticular calcium transport in diabetic cardiomyopathy. *Am J Physiol*. **244**(6):E528-35 (1983).
10. Choi, K. M, Zhong Y, Hoit B.D, Grupp I. L, Hahn H. and Dilly K.W. Defective intracellular Ca<sup>2+</sup> signaling contributes to cardiomyopathy in Type 1 diabetic rats. *American Journal of Physiology, Heart and Circulatory Physiology*, **283**: H1398–H1408 (2002).
11. Dhalla, N.S, Liu X, Panagia V. and Takeda N. Subcellular remodeling and heart dysfunction in chronic diabetes. *Cardiovasc Res.*, **40**: 239-47 (1998).
12. Netticadan, T, Temsah R.M, Kent A, Elimban V. and Dhalla N.S. Depressed levels of Ca<sup>2+</sup>-cycling proteins may underlie sarcoplasmic reticulum dysfunction in the diabetic heart. *J Diabetes*, **50**(9): 2133-8 (2001).
13. Yaras, N, Ugur M, Ozdemir S, Gurdal H, Purali N, Lacampagne A, Vassort G. and Turan B. Effects of Diabetes on Ryanodine Receptor Ca Release Channel (RyR2) and Ca Homeostasis in Rat Heart Diabetes., **54**: (2005).
14. Bilginoglu, A, Kandilci H.M. and Turan B. Intracellular Levels of Na<sup>+</sup> and TTX-sensitive Na<sup>+</sup> Channel Current in Diabetic Rat Ventricular Cardiomyocytes. *Cardiovasc Toxicol*, **13**:138–147 (2013). DOI 10.1007/s12012-012-9192-9.
15. Prodan, E, Kohn W. Nearsightedness of electronic matter. *Proc. Natl. Acad. Sci.*, **110**(46): 18368-18373 (2013).
16. Chandrashekharaiah, K.S. Antioxidant and Type II Diabetes-related Enzyme Inhibition Properties of Few Selected Medicinal Plants. *Biomed Pharmacol J.*, **6**(2):341-347 (2013).
17. Nagareddy, PR, Vasudevan H, McNeill JH. Oral administration of sodium tungstate improves cardiac performance in streptozotocin-induced diabetic rats. *Can J Physiol Pharmacol.*, **83**(5): 405-411 (2005).
18. Wang, XL, Li T, Li JH, Miao SY, Xiao XZ. The effects of resveratrol on inflammation and oxidative stress in a rat model of chronic obstructive pulmonary disease, *Molecules*, **22**(9):1529 (2017).
19. Leporini, L, Giampietro L, Amoruso R, Ammazalorso A, Fantacuzzi M, Menghini L, Maccallini C, Ferrante C, Orlando G, De Filippis B. In vitro protective effects of resveratrol and stilbenealkanoic derivatives on induced oxidative stress on C2C12 and MCF7 cells, *J Biol Regul Homeost Agents.*, **31**(3) (2017). [Epub ahead of print]
20. Wang, B, Fu J, Yu T, Xu A, Qin W, Yang Z, Chen Y, Wang H. Contradictory effects of mitochondria- and non-mitochondria-targeted antioxidants on hepatocarcinogenesis by altering DNA repair, *Hepatology.*, 2017. [Epub

- ahead of print]
21. Nasseri, E, Mohammadi E, Tamaddoni A, Qujeq D, Zayeri F, Zand H. Benefits of Curcumin Supplementation on antioxidant status in  $\beta$ -thalassemia major patients: A double-blind randomized controlled clinical trial, *Ann NutrMetab.*, **71**(3-4): 136-144 (2017).
  22. Mansour, AT, Goda AA, Omar EA, Khalil HS, Esteban M $\acute{A}$ . Dietary supplementation of organic selenium improves growth, survival, antioxidant and immune status of meagre, *Argyrosomus regius*, juveniles, *Fish Shellfish Immunol.*, **68**: 516-524 (2017).
  23. Cupp-Sutton, KA, Ashby MT, Biological chemistry of hydrogen selenide, *Antioxidants*, **5**(4): pii: E42 (2016).
  24. Turan, B, Dhalla NS. Diabetic cardiomyopathy biochemical and molecular mechanisms. Springer-Verlag New York;2014.
  25. Shenasa, M, Nattel S. Cardiac potassium channel disorders, an issue of cardiac electrophysiology clinics. Elsevier;2016.
  26. Ayaz, M, Ozdemir S, Ugur M, Vassort G, Turan B. Effects of selenium on altered mechanical and electrical cardiac activities of diabetic rat. *Arch BiochemBiophys.* **426**(1):83-90 (2004).
  27. Ezaki, O. The insulin-like effects of selenate in rat adipocytes. *J Biol Chem.*, **265**(2): 1124-1128 (1990).
  28. Turan, B. A Comparative summary on antioxidant-like actions of timolol with other antioxidants in diabetic cardiomyopathy, *Curr Drug Deliv.*, ; **13**(3): 418- 423 (2016).
  29. Yaras, N, Ugur M, Ozdemir S, Gurdal H, Purali N, Lacampagne A, Vassort G, Turan B. Effects of diabetes on ryanodine receptor Ca release channel (RyR2) and Ca<sup>2+</sup> homeostasis in rat heart, *Diabetes*, **54**(11): 3082-3088 (2005).
  30. Ayaz, M, Turan B. Selenium prevents diabetes-induced alterations in [Zn<sup>2+</sup>] i and metallothionein level of rat heart via restoration of cell redox cycle. *Am J Physiol Heart Circ Physiol.*, **290**(3):H1071-1080 (2005).
  31. Ozturk, N, Olgar Y, Ozdemir S. Trace elements in diabetic cardiomyopathy: An electrophysiological overview. *World J Diabetes*, **4**(4): 92–100 (2005).
  32. Ayaz, M, Ozdemir S, Yaras N, Vassort G, Turan B. Selenium-induced alterations in ionic currents of rat cardiomyocytes. *BiochemBiophys Res Commun.*, **327**(1):163-173 (2005).
  33. Xu, T, Liu Y, Deng Y, Meng J, Li P, Xu X, Zeng J. Insulin combined with selenium inhibit p38MAPK/CBP pathway and suppresses cardiomyocyte apoptosis in rats with diabetic cardiomyopathy, *Xi Bao Yu Fen ZiMian Yi XueZa Zhi.* **32**(7): 926-930 (2016).
  34. Bilginoglu, A, Seymen A, Tuncay E, Zeydanli E, Aydemir-Koksoy A, Turan B. Antioxidants but not doxycycline treatments restore depressed beta-adrenergic responses of the heart in diabetic rats. *Cardiovasc Toxicol.*, **9**(1):21-29 (2009).
  35. Vural, P, Kabaca G, Firat RD, Degirmencioglu S. Administration of selenium decreases lipid peroxidation and increases vascular endothelial growth factor in streptozotocin induced diabetes mellitus, *Cell J.*, **19**(3):452-460 (2017).
  36. Dhanya, BL, Swathy RP, Indira M. Selenium downregulates oxidative stress-induced activation of leukotriene pathway in experimental rats with diabetic cardiac hypertrophy, *Biol Trace Elem Res.* **161**(1):107-115 (2014).
  37. Joseph, J, Loscalzo J. Selenistasis: epistatic effects of selenium on cardiovascular phenotype. *Nutrients*, **5**(2):340-358 (2013).
  38. Farrokhian, A, Bahmani 2, Taghizadeh M, Mirhashemi SM, Aarabi MH, Raygan F, Aghadavod E, Asemi Z. Selenium supplementation affects insulin resistance and serum hs-CRP in patients with type 2 diabetes and coronary heart disease, *HormMetab Res.*, **48**(4):263-268 (2016).
  39. Alehagen, U, Aaseth J, Johansson P. Reduced cardiovascular mortality 10 years after supplementation with Selenium and Coenzyme Q10 for four years: follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly citizens, *PLoS One.*, **10**(12):e0141641 (2015).
  40. Turan, B, Saini HK, Zhang M, Prajapati D, Elimban V, Dhalla NS. Selenium improves cardiac function by attenuating the activation of NF-kappaB due to ischemia reperfusion injury, *Antioxid Redox Signal.*,

- 7(9-10):1388-1397 (2005).
41. Deng, W, Xie Q, Wang H, Ma Z, Wu B, Zhang X. Selenium nanoparticles as versatile carriers for oral delivery of insulin: Insight into the synergic antidiabetic effect and mechanism, *Nanomedicine*, **13**(6):1965-1974 (2017).
42. Ahmed, HH, Abd El-Maksoud MD, Abdel Moneim AE, Aglan HA. Pre-clinical study for the antidiabetic potential of selenium nanoparticles. *Biol Trace Elem Res.*, **177**(2): 267-280 (2017).