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Review

Homeostatic effect of laughter on diabetic cardiovascular complications: The myth turned to fact



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ABSTRACT

Aims: Laughter has been used for centuries to alleviate pain in morbid conditions. It was not until 1976 that scientists thought about laughter as a form of therapy that can modulate hormonal and immunological parameters that affect the outcome of many serious diseases. Moreover, laughter therapy was shown to be beneficial in type 2 diabetes mellitus (T2DM) by delaying the onset of many diabetic complications. Laughter is also described to influence the cardiovascular and endothelial functions and thus may protect against diabetic cardiovascular complications. In this review, we outline the different biochemical, physiological and immunological mechanisms by which laughter may influence the overall state of wellbeing and enhance disease prognosis. We also focus on the biological link between laughter therapy and diabetic cardiovascular complications as well as the underlying mechanisms involved in T2DM.

Methods: Reviewing all the essential databases for “laughter” and “type 2 diabetes mellitus”.

Results: Although laughter therapy is still poorly investigated, recent studies show that laughter may retard the onset of diabetic complications, enhance cardiovascular functions and rectify homeostatic abnormalities associated with T2DM.

Conclusions: Laughter therapy is effective in delaying diabetic complications and should be used as an adjuvant therapy.

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1. Background

Homeostasis is a dynamic process that drives the function of the human body. Homeostasis depends mainly on the collaboration between the nervous system, hormones secreted by endocrine glands and the immune system. Together, they form the intercommunication loop between the mind and the body. Therefore, homeostasis is influenced by mental, physical and chemical factors including the emotional state of the individual. In this review, we will focus on laughter as a positive emotion that can regulate homeostasis and may, to some extent, alleviate the abnormal homeostatic state associated with type 2 diabetes mellitus (T2DM). The therapeutic potential of laughter medicine in delaying the complications of T2DM will be explored.

2. History of laughter therapy

Laughter therapy is as old as the bible itself. A biblical proverb states that “a merry heart doeth good like a medicine” (Proverbs 17:22, King James Bible). This verse was the first to address the health benefits of laughter and joy as noted by Martin in 2001 [1]. Both physicians and philosophers in the 16th century appreciated the value of laughter in promoting health [2]. In another review [3], Hassed cited a quotation from the 17th century that emphasized on the therapeutic value of laughter, “The arrival of a good clown exercises more beneficial influence... than that of 20 asses laden with drugs”. Hassed also quoted Immanuel Kant, the 18th century philosopher who “considered laughter useful for restoring equilibrium” [3].

We have to differentiate between humor and laughter as two separate terms. The Oxford English Dictionary defines humor as “that quality of action, speech, or writing which excites amusement; oddity, jocularly, facetiousness, comicality, fun” [4]. Humor is a very broad concept and it involves cognitive, behavioral, emotional, psychophysiological, and social aspects [1]. Martin (2001) described three ways of using the term “humor”. It can be used to refer to a stimulus (for instance, a comedy film) or a mental process (for instance, perception or creation of amusing incongruities), or finally a response (e.g., laughter) [1]. Laughter, on the other hand, is the behavioral expression of humorous experience. Laughter involves a distinctive respiratory-vocal-behavioral pattern [5,6]. Humor and laughter are both associated with a pleasant emotional state [7]. In this review, we will use humor and laughter interchangeably for convenience as all the cited

studies used humor-stimulated mirthful laughter except if otherwise stated.

For many centuries, people appreciated the value of laughter in oncology, critical care, mental health, hospice, and health promotion such that anecdotes of using laughter and humor in treatment gained much popularity [2]. There are reported cases where laughter therapy was shown to improve the clinical outcomes of disorders such as inflammation, asthma, cancer, and heart disease [3]. This was shown to commence mainly through the reduction of the physiological stress response, which is an exacerbating factor in these conditions. Additionally, studies have reported that laughter therapy may alleviate stress and anxiety levels, improve mood and self-esteem, enhance coping skills and increase pain tolerance [8].

3. Homeostasis and therapeutic mechanisms of laughter

Laughter, as a form of psychotherapy, gained much attention after Norman Cousins successfully cured himself from ankylosing spondylitis by laughter in 1976 [9]. Cousins observed that negative stress or over-fatigue was the main underlying cause for this disease. He then suggested that positive emotion e.g. laughter could reverse his condition and tested this hypothesis on himself. The results of Cousins test support the therapeutic potential of laughter.

By practicing laughter as a therapeutic approach, Cousins experienced painless sleep and his erythrocyte sedimentation rate was attenuated; indicative of inflammation regression. However, in Cousins’ latter review, he argued that the therapeutic value of laughter was related to the psychological abatement of panic rather than biochemical alterations [10].

The limitations of Cousins study included the co-administration of vitamin C which may have contributed to the observed improvement. Despite that, scientists were encouraged to further investigate laughter therapy and its biochemical manifestations [9]. Early studies by Berk et al. (1989) investigated the immunological effects of laughter. The data showed that laughter improved the activity of natural killer cells related to tumor immunity and decreased blood cortisol levels related to stress [11]. This emphasized the association between laughter and the neuroendocrine immune axis.

The neuroendocrine immune axis is described to predominantly link the catecholamine nerves, the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA)

axis [12]. The amelioration of stress upon laughter therapy may therefore be related to a hijacking of the neuroendocrine stress loop. Berk et al. examined the involvement of HPA axis by recording measurements of stress hormone levels in blood prior to and after subjects were exposed to 60-min comedy videos [13]. The results showed that laughter significantly decreased cortisol level in the blood (stress index) in addition to the concentration of 3,4-dihydroxyphenylacetic acid (DOPAC), which is the major metabolite of dopamine. Moreover, blood epinephrine levels were also reported to be lowered even before exposure to the comedy video; indicative of the anticipation participants. Additionally, growth hormone levels were also measured and reported to be seven folds increased in comparison to baseline values [13].

Meanwhile, Berk et al. demonstrated a lack of correlation in NK- cell activity and the magnitude of laughter evident by the profile of mood states (POMS) negative score. In contrast, a latter study reported a significant correlation between laughter and NK-cell activity [14]. The stress reduction potential of laughter was further proved by Toda et al., (2007) [15]. Their group investigated the effect of laughter on salivary chromogenin A (CgA). CgA is an acidic glycoprotein that is secreted by the adrenal glands and sympathetic nerve endings associated with catecholamines, and is considered a biomarker for stress [16–18]. It was found that CgA is secreted by submandibular salivary glands in the saliva [19] and its salivary levels are correlated specifically with mental stress but not physical stress [20,21]. Toda et al. recruited 11 healthy subjects who were exposed to either landscape scenes for 30 min or a comedy show on different days and their salivary CgA levels were measured using enzyme-linked immunosorbent assay (ELISA) prior to and after exposure in addition to a time point 30 min after the experiment. Subjects who viewed the landscape video did not experience any difference in salivary CgA levels while subjects who viewed the comedy show experienced an increase in the levels of salivary CgA after the show. Elevated CgA levels are known to be correlated with positive or negative stress (eu-stress and di-stress respectively). The results showed an elevation of CgA after the comedy show which allows the deduction that elevated CgA may be due to eu-stress, which was confirmed by the evaluation of subjective stress perception using a visual analog scale [15].

Another research group focused on another aspect of the homeostatic system that may be influenced by laughter which is blood pressure. Fry and Savin (1988) investigated the effect of mirthful laughter on blood pressure [22]. Since laughter is composed of two physiologic elements, respiratory and muscle activity, it may influence blood pressure by affecting mechanical and hydrodynamic factors. The study by Fry and Savin recruited 15 men from heterogeneous cardiovascular groups and exposed them to a 15-min audio track with comical content over 14 episodes. The arterial blood pressure of the participants was continuously recorded by the insertion of an arterial catheter and strip chart recorder. The final episode of the experiment included exposure to a 30-min comedy movie to investigate the effect of video stimulus and compare it to the audio stimulus. The results showed that laughter, whether associated with mirth or stim-

ulated, is accompanied by an initial abrupt increase in systolic and diastolic blood pressure followed by a gradual decrease in blood pressure below pre-laughter levels [22]. Off note, the authors neglected any hormonal effect. They have not assessed the levels of stress hormones or linked them to blood pressure.

Fry and Savin's study paved the way for all laughter-based clinical experiments. Their vigilance about key variables affecting laughter experiments set the standard for the following experiments. A distinction between mirthful and stimulated laughter was one of the key features emphasized by the study. Stress avoidance was also deduced from the study by selecting audio skits that did not include any offensive content. Thirdly, study environment was meticulously arranged so that caregivers shared in the mirth, incorporating the humor-potential effect and creation of the "play" mood [22].

With regards to the immune system, laughter was shown to affect a range of immunological factors. Laughter was reported to increase the levels of immunoglobulins A, G, M and complement C3 in addition to the levels of surface markers CD3+DR+ (activated T-cell marker), CD57+CD8+ (T-cell marker), CD19+ (B-cell marker), and the CD4-CD8 ratio [23]. The immunological effect of laughter may, thus, be central to the alleviation of many inflammatory conditions. For instance, in rheumatic patients, laughter managed to decrease IL-6 levels [24,25] and to reduce pain in arthritis [24].

Similarly, the effect of laughter on the immune system was also studied in atopic keratoconjunctivitis patients. The study reported that laughter decreased the allergen-specific IgE, IgG4 and increased IgA concentration in tears [26]. This effect may be attributed to the reduction of nerve growth factor (NGF) [26]. NGF is believed to increase during stress elevating the levels of IgE, IgG4 and reducing IgA levels [27]. The increase in IgA concentration may be one of the mechanisms by which laughter ameliorates allergic reactions as it is reported that IgA inhibits allergic reactions [28]. Moreover, it was previously described by Kimata that laughter also inhibited IgE-mediated wheal and flare allergic reactions [29,30].

Another homeostatic mechanism for laughter therapy is that it can decrease reactive oxygen species (ROS). Atsumi et al. observed that exposure to an amusement video increased salivary free radical scavenging activity (FRSA) systems which was inversely proportional to ROS levels ($P < .001$) in a study that involved 36 healthy subjects [31]. ROS have been described to be involved in the pathogenesis of chronic inflammatory diseases and cancer, as well as in aging [32]. The effect of laughter on the prognosis of these conditions is therefore an interesting therapeutic approach. Yet, a direct correlation between laughter and ROS reduction in these condition was not established and stays empirical.

Rising literature explores the various mechanisms of laughter therapy and describes the influence of laughter on the physiological mechanisms. Laughter was found to exercise and relax muscles, improve respiration, stimulate circulation, decrease stress hormones, increase the immune system's defenses, elevate pain threshold and tolerance, and enhance mental functioning [33–35].

4. Laughter therapy in type 2 diabetes mellitus

We sought to review the effect of laughter on T2DM. To achieve this aim, we have searched all major databases by selecting both the MeSH terms “laughter” and “type 2 diabetes mellitus” and keywords “laughter and “type 2 diabetes mellitus”.

Laughter can affect the most prominent abnormality associated with T2DM which is postprandial glucose levels as reported by Hayashi et al. [36]. In this study, 19 diabetic patients were recruited for 2 days, during which fasting blood glucose levels were monitored while the subjects adhered to their standardized 500 kcal lunch. All subjects attended a monotonous lecture for 40-min on the first day, and on the second day they were exposed to a comedy show for the same duration among 1000 additional participants (to add to the environment’s humor-potential). Results revealed that postprandial glucose levels increased by 123 mg/dL on the first day while the increase was averaged at 77 mg/dL on the second day which meant a 46 mg/dL decrease in blood glucose levels due to laughter ($p < .005$). Unfortunately, the authors neglected to report the changes in circulating insulin levels. Although the reported results were promising, there was no long-term follow up to investigate the constancy of this hypoglycemic effect.

Murakami and Hayashi investigated negative stress controls and gene expression of transcription factors involved in the neuroendocrine immune axis [37]. The effect of positive emotions, especially laughter, on this axis was also examined in the context of T2DM. Similar to their previous study [36], 12 diabetic patients were subjected to a laughter stimulating experience on the first day and a monotonous lecture on the second [38]. In this study, fasting and postprandial glucose levels were measured and the obtained results resonated with the previous study. As for the gene expression patterns, blood samples were collected for analysis from patients before and 1.5 h after the laughter intervention. They labeled the pre-intervention mRNA with Cy3 and the postintervention mRNA with Cy5 and then they mixed equal parts of the pre- and post-intervention mRNA. Agilent Human 1A microarray was used to carry out competition binding reaction and confocal laser scanner was used to read the signal of fluorescence intensity of each dye. Bonferroni correction multiplex analysis was used to discriminate genes exhibiting significant relative changes in expression compared to that observed after monotonous lecture. Of the 18,716 genes tested, there was alteration in gene expression of 23 genes with 8 upregulated genes and 15 downregulated genes. Of the 23 altered genes, 18 were previously known. Of the downregulated genes, 4 genes were involved in the immune system and 4 in signal transduction while the upregulated genes were involved in cell cycle, apoptosis and cell adhesion. Surprisingly, genes involved in blood glucose levels regulation were unaltered. Despite that this experiment shed the light on the effect of laughter on gene expression in T2DM, it is limited by the short duration of the intervention (only 40 min), the lack of gene annotation of the altered genes and the small sample size.

A follow-up experiment was conducted by Hayashi et al. [39]. Ten patients with T2DM were recruited for a two-day experiment. Patients were presented with their prescribed meal and then with a diabetes-related lecture on day one. On day two, the patients were asked to watch a comic show for 1 h. Blood samples were collected at baseline, immediately after the show, 1.5 h and 4 h after the show or the lecture. For gene expression analysis, Agilent Whole Human Genome microarray technology was used which included 41,000 genes. Twenty-seven genes were upregulated for 4 h as indicated after discrimination of genes that were observed to change 1.25 folds in 1.5 h and 1.5 times in 4 h following the laughter experience. On the other hand, no genes were observed to be downregulated. Only 15 of the 27 upregulated genes were related to immunity with all except one associated with NK-cell activity. NK cells are strongly associated with glucose tolerance which was assessed by the adoptive transfer of NK cells into ob/ob mice which resulted in marked enhancement of glucose tolerance [40]. Elinav et al. also showed that increasing the levels of intrahepatic NK cells is associated with enhanced glucose tolerance [41]. Therefore, we can safely conclude that laughter exerts its beneficial effects in T2DM through, at least partially, modulating NK-cell activity and upregulating genes related to its function. However, there was no assessment for any biological outcome related to this beneficial effect.

T2DM perturbs the renin-angiotensin system (RAS) which can predispose hypertension and nephropathy [42–44]. Nasir et al. investigated the effect of laughter on RAS in patients with T2DM [45]. In this study, 18 patients were recruited with T2DM. Patients viewed comedy movies once a week (30–40 min) for six months. Blood samples were collected before the beginning of the study, after 3 months and after six months for the measurement of renin, angiotensin I and prorenin plasma levels by ELISA. The mean plasma renin concentrations were 24.6 ± 12.1 ng/ml/h at baseline which laughter therapy reduced to 8.2 ± 3.4 ng/ml/h after 3 months and 7.7 ± 1.7 ng/ml/h after 6 months. The mean plasma angiotensinogen concentrations were 0.19 ± 0.08 g/ml at baseline which were increased and restored to normal levels (0.47 ± 0.12 g/ml after 3 months and 0.42 ± 0.14 g/ml after 6 months). There were no significant changes in the mean plasma prorenin concentrations at baseline, after 3 months and after 6 months ($195.1 + 66.2, 193.4 \pm 88.2$ and $170.7 + 52.5$ pg/ml, respectively). This was the *first and only* long-term study done for laughter therapy on patients with T2DM and it proved that laughter therapy can be an adjunct therapy to protect from diabetic microvascular complications.

Another more recent study provided evidence for this protective potential [46]. This time, the authors selected blood prorenin level which can be used a marker of microvascular complications [47] and its activation is correlated with diabetic nephropathy [48]. Once again, Hayashi et al. designed an experiment to test this hypothesis [46]. This time, 23 patients with T2DM were divided into 12 nephropathy (-) and 11 nephropathy (+) patients and 16 normal controls. For all subjects, prorenin and prorenin receptor gene expression were analyzed using ELISA and RT-PCR respectively. All sub-

jects attended a 40-min Japanese comedy show together with 1100 participants immediately after lunch and blood samples were collected directly after, and 1.5 h after watching the show for baseline determination, blood prorenin assay, and gene expression analysis. As expected, prorenin levels were higher in patients with T2DM in both nephropathy (–) (93.4 ± 33.7 ng/l; $P = .002$) and nephropathy (+) patients (196.6 ± 127.4 ng/l; $P = .001$) compared to control subjects (32.5 ± 11.6 ng/l). Those high levels were reversed 1.5 h after the laughter experience (60.4 ± 31.2 ng/l; $P = .006$) in nephropathy (–) patients. On the other hand, there was no significant decreases in normal subjects and nephropathy (+) patients. Results also showed that the expression of prorenin receptor gene was less active in patients with T2DM whether they were nephropathy (+) or (–) compared to control (nephropathy (–) patients, 82.9 ± 11.6 , $P = .013$; nephropathy (+) patients, 76.0 ± 17.7 , $P = .004$; normal subjects, 99.1 ± 13.4). Laughter succeeded in normalizing this gene expression in patients with T2DM (nephropathy (–) patients, 123.4 ± 34.7 , $P = .003$; nephropathy (+) patients, 111.2 ± 30.8 , $P = .008$), however, it did not affect this gene expression in control (97.1 ± 28.2).

While blood prorenin level is associated with microvascular complications [47], prorenin receptor is associated with cognitive functions [49]. It can be deduced that laughter protects against microvascular complications associated with T2DM as reflected by decreased prorenin levels and protects against diabetic dementia and neurodegenerative complications as reflected through normalizing the expression of the prorenin receptor genes in peripheral blood leukocytes [46]. Bains et al. investigated the effect of laughter on enhancing short-term memory of patients with T2DM and consequently on delaying neurodegenerative complications of T2DM [50].

Deterioration of cognitive function is a major complication in T2DM [51–54] but the exact mechanisms of this dysfunction have not been elucidated yet [55]. Dementia is a possible insult in T2DM as a reduction of the volume of hippocampal gray matter due to depression may occur [56], in addition to poor glucose control [57,58] and chronic life stress [59]. Another hypothesis suggests that cortisol is considered to be neurotoxic to the hippocampus, the site of consolidated memory, so laughter which is known to reduce stress by decreasing the levels of cortisol may protect against dementia [13,23]. The study by Bains et al. included 20 normal healthy subjects and 10 patients with T2DM. The study included two groups (one healthy and the other with T2DM) who viewed a humorous video for 20-min and a control group that did not watch the video and sat in quiescence. Following that, a standardized neuropsychological memory-assessment tool

(the Rey Auditory Verbal Learning Test “RAVLT”) was used to assess learning, recall and visual recognition. This test was conducted before and after the viewing or the quiescence period. Salivary cortisol was also measured at 5 different time points.

In the healthy humor, T2DM, and control groups, the learning ability improved by 38.5%, 33.4%, and 24.0%, respectively ($P = .025$) while the delayed recall improved by 43.6%, 48.1%, and 20.3%, respectively ($P = .064$); and finally the visual recognition increased by 12.6%, 16.7%, and 8.3%, respectively ($P = .321$). It is evident that the groups who viewed the comedy video had enhanced short-memory functions. Laughter also decreased the levels of salivary cortisol in the study groups [50]. Future studies are warranted in this area that should include additional outcome assessment techniques like functional magnetic resonance imaging (fMRI) to further support this beneficial effect. The effect of laughter on diabetic complications and the associated pathways are summarized in Table 1.

5. Laughter and cardiovascular complications

For decades, it was believed that people who experience humor in their everyday life are less likely to suffer from stress. This negative association was investigated by Clark et al. where a Situational Humor Response Questionnaire (SHRQ) was provided to 300 volunteers (patients with coronary heart disease (CHD) and controls) and their answers were later analyzed. Results showed that CHD patients were less likely than non-CHD subjects to find certain situations that may be encountered to be humorous ($P < .005$). Logistic regression analysis showed an inverse correlation between CHD and humor, even after adjustment for hypercholesterolemia, hypertension and diabetes mellitus ($P = .03$) [60].

Laughter can also affect arterial stiffness and central hemodynamics. In a study, 18 healthy subjects viewed a comedy video for 30 min, and the results showed that laughter reduced pulse wave velocity (by 0.30 m/s, $p < .01$), and augmentation index (by 2.72%, $p < .05$) which reflects arterial elasticity. Both large artery stiffness and wave reflections are determinants of left ventricular function and mechanical integrity of arteries and since they are both deteriorated in T2DM [61], laughter can be beneficial in delaying cardiovascular complications of T2DM. However, a study that involves patients with T2DM has never been done to support this hypothesis.

Another study reported that brachial vasodilatation (assessed by brachial artery reactivity testing “BART”) was

Table 1 – The effect of laughter on type 2 diabetes mellitus and its associated complications. HPA: hypothalamus-pituitary-adrenal, NK: Natural-killer, RAS: renin-angiotensin system.

Parameter	Pathway	Reference
Postprandial blood glucose	HPA axis	[36,38]
Immunity	NK cell gene expression, cell cycle, apoptosis and cell adhesion	[38,39,41]
Nephropathy	RAS and prorenin receptor gene expression	[45,46]
Neurodegenerative complications	Enhancing short-term memory and lowering cortisol levels	[50]
Cardiovascular complications	Blood pressure, RAS, endothelial and cardiovascular functions	[22,45,60,70]

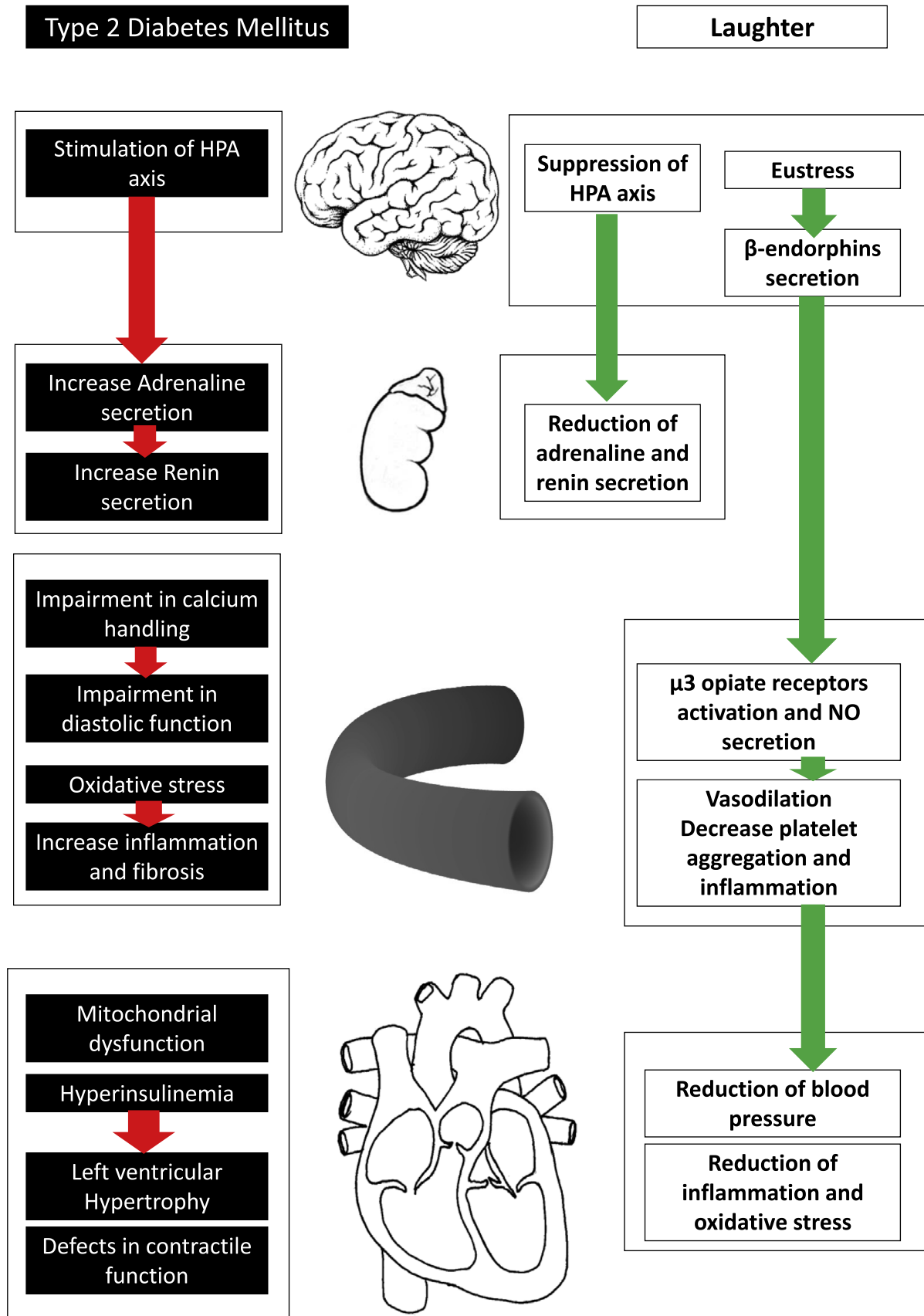


Fig. 1 – Mechanisms of laughter in cardiomyopathy. HPA: hypothalamus-pituitary-adrenal.

increased in 19 of 20 volunteers after watching a 30-min comedy video that generated laughter ($p < .0001$). There were also significant (22%) increase in flow mediated dilation (FMD) after the viewing of the comedy video ($p < .0001$) suggesting that laughter can alter endothelial function [62]. The Brachial artery reactivity testing is a non-invasive tool that has been used in the evaluation of CV risk factors and response to therapy [63–66]. The reported results were similar to that previously observed with aerobic activity [67] or statin therapy [66]. On the other hand, Miller et al. reported a marginally significant effect of laughter on brachial artery flow mediated vasodilation ($p < .08$) in a study involving 10 healthy volunteers [68]. More studies are warranted to resolve this controversy.

Further evidence on the effect of laughter on endothelial function was provided by Sugawara et al. In their study, seventeen healthy subjects watched 30 min of a comedy show or a documentary on separate days. Results showed an increase in heart rate and blood pressure while watching the comedy, but not while watching the documentary. The investigators used B-mode ultrasound imaging to measure ischemia-induced brachial artery flow-mediated vasodilation and it was found to be significantly increased after watching the comedy (17%) while it actually decreased with exposure to the documentary (–15%). Carotid arterial compliance was assessed by simultaneous application of ultrasound imaging and applanation tonometry and it was found to be increased by 10% immediately after watching the comedy and returned to baseline after 24 h, whereas the control group did not show that kind of change. These reported results suggest a beneficial impact of laughter on vascular function [69].

A representation of the effect of laughter on endothelial function was proposed by Miller and Fry [70]. Laughter would influence hypothalamus and pituitary gland to secrete beta endorphins (or other opioid-like compounds) which will reach vascular endothelium and interact with the μ_3 opioid receptor inducing the release of nitric oxide [71] which in turn will cause vasodilation, reducing inflammation and platelet aggregation, and inhibition of leukocyte trafficking via cellular signaling pathways that include a cGMP-dependent pathway [72].

Recently, Hayashi et al. investigated the effect of laughter on the prevalence of cardiovascular diseases [73]. In their study, they evaluated the association between daily laughter with heart disease and stroke. This study involved 20,934 individuals (10,206 men and 10,728 women) who aged 65 or older. Data were collected via mail-in survey, where participants provided information on daily frequency of laughter, body mass index, demographic and lifestyle factors, and diagnoses of cardiovascular disease, hyperlipidemia, hypertension, and depression. Results revealed that the prevalence of heart disease was 1.21 (95% CI, 1.03–1.41) times higher in subjects who never or barely laughed than in subjects who laughed every day even after adjustment for hyperlipidemia, hypertension, depression, body mass index, and other risk factors. Similarly, the prevalence ratio for stroke was 1.60 (95% CI, 1.24–2.06) times higher in subjects who never or almost never laughed than in subjects who laughed every day [73]. Notwithstanding that these results showed a signif-

icant difference, data collection was highly subjective and depended only on the patient's assessment and input. We also cannot neglect that few people have suffered a stroke during laughter due to the sudden elevation of blood pressure [22].

Collectively, the previous studies provide a strong evidence for the beneficial effect of laughter on the cardiovascular system (Fig. 1). The reported benefits suggest that laughter can be extremely useful as an adjuvant therapy to retard cardiovascular complications of T2DM. However, more research is required to investigate the various mechanisms by which laughter can enhance the vascular function and retard cardiovascular diseases. Clinical studies that investigate the effect of laughter on the development of cardiovascular complications in patients with T2DM are also critical to further our understanding. Although the benefits of laughter on blood pressure [22], RAS [45] and cardiovascular functions [60] are well documented in literature, to date there are no studies on laughter in enhancing the cardiovascular outcome associated with T2DM.

6. Conclusion

In conclusion, laughter can greatly enhance the quality of life of patients with T2DM. Evidences from various clinical and experimental studies showed that laughter can decrease blood glucose levels, blood pressure levels and protect against complications associated with T2DM. Many diverse mechanisms have been attributed to laughter action in T2DM. These mechanisms include the neuroendocrine immune axis, HPA axis, altering gene expression of NK immune cell genes, prorenin receptor genes and other genes involved in cell cycle, apoptosis and signaling. Collectively, these mechanisms work on the mind-body communication loop both directly and indirectly [74]. Most of the reported studies focused on short-term effects of laughter, so we encourage the design of long-term studies that can identify with the chronicity of T2DM. We also recommend benefiting from those studies by coining guidelines about the alteration of the lifestyle of patients with T2DM e.g. emphasizing the importance of laughter for these patients and recommending daily comedic inclusions for a fixed time every day, advising against stressful and monotonous conditions and prescribing humor therapy, laughter therapy, laughter meditation, and laughter clubs as group programs and as self-management techniques.

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Compliance with Ethical Standards

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Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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