Traumatic experiences and type 2 diabetes mellitus

Esperienze traumatiche e il diabete mellito di tipo 2

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SUMMARY. Introduction. Type 2 diabetes mellitus (T2DM) is a complex and demanding chronic condition resulting from the body's inability to adequately produce and or effectively utilize insulin. A wide variety of lifestyle factors are of great importance to the development of T2DM, such as sedentary lifestyle, obesity, physical inactivity, smoking and alcohol consumption. An emerging body of literature suggests that stress and traumatic experiences have a role in the aetiology of T2DM. **Methods.** We recruited a sample of 52 patients with a diagnosis of T2DM and a control group of 48 subjects. Using the Traumatic Experience Checklist (TEC), the Childhood Experience of Care and Abuse Questionnaire (CECA-Q), and the Connor-Davidson Resilience Scale (CD-RISC 25), we investigated the presence of history of traumatic experiences and of childhood experience of neglect and abuse. **Results.** We found that patients with a diagnosis of T2DM have a higher number of traumatic experiences in their personal history, when compared to the control group. **Discussion.** Traumatic experiences or sustained stress exposure may contribute to the onset of T2DM. Neuro-inflammatory and psychoanalytic factors will be discussed to explain such association. **Conclusion.** We conclude that factors that determine high levels of resiliency can have a protective effect against the development of T2DM while stress and the consequent inflammation can contribute to the development of depression and T2DM. These biological features are analyzed in the psychoanalytical context of theories from Freud, Mahler, and Kohut.

KEY WORDS: type 2 diabetes mellitus, trauma, resilience, adverse childhood experiences, ACE.

RIASSUNTO. Introduzione. Il diabete mellito di tipo 2 (T2DM) costituisce una condizione cronica complessa e impegnativa, conseguente all'incapacità del corpo di produrre adeguatamente l'insulina e/o di utilizzarla efficacemente. Un'ampia gamma di modalità di stili di vita come la sedentarietà, l'obesità, il fumo e il consumo di alcol sono di rilevante importanza nello sviluppo del T2DM. Una consistente mole di letteratura recente suggerisce che lo stress e le esperienze traumatiche abbiano un ruolo nell'eziologia del T2DM. **Metodi.** Abbiamo reclutato un campione di 52 pazienti con diagnosi di T2DM e un campione di controllo di 48 soggetti. Abbiamo applicato il Traumatic Experience Checklist (TEC), il Childhood Experience of Care and Abuse Questionnaire (CECA-Q) e il Connor-Davidson Resilience Scale (CD-RISC 25) per indagare la presenza di una storia di esperienze traumatiche ed esperienze infantili di trascuratezza e abuso. **Risultati.** Abbiamo concluso che i pazienti con diagnosi di T2DM hanno un numero maggiore di esperienze traumatiche nella loro storia personale, comparati al gruppo di controllo. **Discussione.** Le esperienze traumatiche o di esposizione a stress prolungato possono contribuire all'esordio del T2DM. Viene analizzata la connessione tra i fattori neuroinfiammatori e psicodinamici. **Conclusioni.** Un elevato livello di resilienza può rappresentare un fattore protettivo contro lo sviluppo di T2DM mentre lo stress e la conseguente infiammazione può contribuire a determinare la depressione e il T2DM. Leggiamo questi elementi biologici nell'ottica delle teorie psicoanalitiche di Freud, Mahler e Kohut.

PAROLE CHIAVE: diabete mellito di tipo 2, trauma, resilienza, esperienze infantili avverse, ACE.

INTRODUCTION

There is abundant evidence of the link between stressors and Type 2 Diabetes Mellitus (T2DM) risks and of the inverse proportionality between resilience and T2DM risk, both as a predictor of new onset T2DM and as a prognostic factor in people with existing T2DM. Exposure to chronic or toxic stress is linked to negative physical and psychological health[1]. Chronic stress causes a low-level inflammation, which in turn can lead to cytokine-induced insulin resistance; behavioral mechanisms can also link stress and T2DM risk[2].

According to studies on primates, exposure to moderate psychological stress leads to a depressive reaction, which in turn leads to the development of adverse metabolic indicators such as insulin resistance which explains the relationship between depression and T2DM[3]. Stressors are considered, from an evolutionary viewpoint, to be any life event that interferes with the achievement of short-term biological goals such as: making friends, developing social support networks, attracting a mate, and establishing intimate relationships[4]. Much has been written about the cumulative effect on physical and mental health of chronic activation of the HPA axis, particularly when the exposure to stressors coincides with neural development. The plasticity of neural development includes the ability to modify the phenotype, which is evolutionarily advantageous and the sensitivity to early trauma is

the price to pay for obtaining the developmental plasticity. This adaptive developmental plasticity recognizes various mechanisms, which often includes epigenetic changes[5]. The effects of stress which determine a higher risk of T2DM are the activation of the HPA, epigenetic changes, some lifestyle factors, excessive cortisol production, inflammation, insulin resistance, and shortness of telomeres.

Moreover, in accordance with these data, the literature shows a significant increase in T2DM's incidence in subjects with a diagnosis of Post-Traumatic Stress Disorder (PTSD)[6,7]. A prospective study, focusing on Vietnam era veterans who are members of the VET Registry, at baseline used the Diagnostic Interview Schedule (DIS) for assessment of PTSD in 1992 and diagnosis of T2DM between 2010 and 2012[7]. Veterans who were diagnosed with PTSD had a higher rate of metabolic and behavioral risk factors and the level of PTSD was directly proportional to the risk of T2DM. It was found that PTSD seems to be associated with a 40% increased risk of new onset T2DM and this link can be explained in part by a cluster of metabolic and behavioral factors able to determine chronic perturbations of HPA axis. It was concluded that PTSD could be a marker of hormonal and metabolic dysregulation which may lead to insulin resistance and increased risk of T2DM.

A number of studies highlight early psychosocial factors such as childhood adversities, psychological neglect or abuse, socioeconomic status, anxiety, and depression as potential risk factors for T2DM[7]. In a study of 461 participants, of which 55.5% had a T2DM diagnosis at the time of their interview, it was evaluated whether social support matters in association with depressive symptomology and psychological trauma with diabetes control in American Indian women. The researchers measured depressive symptomology with the 20-item Centers for Epidemiological Studies-Depression (CES-D) Scale and used the National Anxiety Disorders Screening Day Instrument to measure psychological trauma and associated symptoms. Information on social support was collected from a survey which was part of the Native Elder Care Study interview with the Medical Outcomes Study Social Support (MOSSS). One of the results of the study was that they observed a trend of higher levels of HbA1c (glycated Hemoglobin) with increasing CES-D scores among participants with low social support. There was also a statistically significant association between psychological trauma and higher HbA1c levels suggesting poorer T2DM control was connected to psychological trauma[8].

In a systematic review which considered the link between psychosocial factors and diabetes incidence or obesity risk, it was found that childhood socioeconomic status seems to have an impact on early family environment, psychosocial functioning, and adult socioeconomic status and is associated with risks of T2DM and obesity later in life. Some of the social and psychological conditions which were observed in the participants and were linked to the increased risk of T2DM include: adverse childhood experiences such as neglect and abuse; childhood depression or anxiety; and resilience indicators[9].

In 2013, a 35-year prospective follow-up study of 7,500 middle-aged men in Sweden was conducted to see if there was a link between perceived stress and diabetes risk. Levels of stress were graded by the participants through a single-question in a questionnaire which identified stress as feeling tense, irritable, full of anxiety, or having trouble sleeping. The questionnaire further separated the category into three groups at baseline: little stress, periodic stress, and permanent stress. Of these participants, those with diabetes were identified through the dismissal records from hospitals or through death registries. At baseline 15.5% of participants reported permanent stress related to work or home life. It was found that men who reported permanent stress had a 45% higher risk of developing diabetes, compared to men who reported to have no (31.2%), or just periodic (31%), stress[2].

There can be a great variety of ways in which people perceive and interpret stressors. These coping strategies can be linked to neuroendocrine responses to acute chronic stress[1]. Resilience is a psychosocial construct that can be described basically as an individual's capacity to maintain psychological and physical well-being when facing adversities. An important, but controversial, question, regards differentiation between resilience and psychopathological elements such as numbness to, or maniacal negation of the stressor[4].

Changes in gene expression can be related to epigenetic changes which prepare the individual for future responses to environmental challenges. As limited exposure to germs can lead to an inoculation against future illness, brief exposure to stress can also lead to a more developed resilience to future stress. There are other factors which also contribute to the development of resilience, in particular, personality and cognitive factors such as positive social relations; self-esteem; sense of hope, respect and esteem for others; interpretation of traumatic experiences as not being their fault; and self-control[1]. Conversely, early severe stressors can impair resilience.

Resilience factors such as personality may be stable over time while others may vary based on changes to life circumstances or the availability of resources[4]. Potentially traumatic life events are often believed to lead to PTSD when the individual has preconceived negative worldviews. In a prospective study it was noted that love, gratitude, and other positive emotions buffered the relation between pre-event ego resilience and post-event depression and perceived growth[4]. Following an evolutionary perspective, some individuals may be more sensitive to stressors, but also more receptive to positive environmental factors due to the similarity of the function of vulnerability genes and developmental plasticity genes[5]. Stress mediators and their related receptors on the hypothalamus-pituitary-adrenal axis are prime targets for epigenetic changes[1].

Various studies have underlined the correlation between resilience, or factors which relate to resilience, with the risk of T2DM. In a follow-up study involving 837 subjects, researchers analyzed the correlation between five personality traits (conscientiousness, agreeableness, openness, neuroticism, and extroversion) and the levels of HbA1c and the polygenic risk of T2DM in order to find whether personality traits moderate the manifestation of Type 2 genetic risks. They used a 60-item NEO Five Factor Inventory to evaluate the five personality factors. The only personality trait related to T2DM polygenic risk was agreeableness[10]. The association between openness and cognitive ability explains the link between openness and HbA1c as cognitive ability moderates the expression of its T2DM risk and has been linked to diabetes onset. The authors concluded that personality traits can affect common genetic variants that predispose one to diabetes. Potential mechanisms of such associations are ele-

ments of lifestyle, such as diet and exercise, and general levels of concern for one's health[10].

A Swedish follow-up study on resilience and risk of T2DM, assessed resilience in healthy, 18-year old military personnel over a 25-year period. The study evaluated the insurgence of T2DM in the 25 years of observation of participants who did not have diabetes at the beginning of the study. It was found that there was an inverse correlation between resilience and T2DM as well as other health risks[11].

The main objective of our study is to verify the hypothesis of an existing correlation between traumatic experiences and T2DM. Moreover, we hypothesize the existence of an inverse correlation between subjects' resiliency and the onset of T2DM.

METHODS

We conducted a case control study. Patients were recruited from the Diabetes Foot Outpatients' Service at the "Policlinico Tor Vergata" in Rome. The patients were recruited after having signed a specific informed consent for the study participation. Exclusion criteria were: 1) use of substances; 2) patients younger than 18 years old; 3) comorbid neurologic disorder that severaly impairs cognitive functioning (i.e. dementia). A control group, matched for age and gender, was recruited.

Every subject involved in the study was asked to complete the following questionnaires:

- Traumatic Experience Checklist (TEC)[12]. The TEC is a self-reporting measure addressing potentially traumatizing events. Preliminary findings suggest that the TEC is a reliable and valid self-report instrument that can be used in clinical practice and research. Different scores can be calculated, including a cumulative score, and scores for emotional neglect, emotional abuse, physical abuse, sexual harassment, sexual abuse, and bodily threat from a person.
- Childhood Experience of Care and Abuse Questionnaire (CECA-Q). The CECA-Q is a questionnaire version of the Childhood Experience of Care and Abuse interview[13]. It covers parental loss, neglect, antipathy (hostile or cold parenting), support, and physical and sexual abuse before age 17 in adolescents or adults. It is validated against the interview measure. Version 2 covers additional psychological abuse and version 3 covers both psychological abuse and role reversal (parentification/young carer). The questionnaire has shown satisfactory reliability and validity as a self-reporting measure for adverse childhood experience.
- Connor-Davidson Resilience Scale (CD-RISC 25)[14]. Resilience was assessed by the Italian version of the CD-RISC-25. This scale contained 25 items responded through a five-point Likert scale. Hence, its scores could range from 0 to 100, with higher scores representing more resiliency. This scale has been validated in several groups, such as general population, individuals who referred to primary care unit, and patients with generalized anxiety disorder and post-traumatic stress disorder. It also showed suitable psychometric properties.

Statistical analysis

Data analysis was conducted through the processing of the results of the administered questionnaires. Non-parametric statistical methods (Mann-Whitney U test) will be used to compare the level of traumatic experiences. For quantitative characters, in addition to the central tendency and variability, mean values and variances will be compared. The significance threshold will be $p < 0.05$. Furthermore, logistic regression analysis was performed to investigate the relationship between the amount of traumatic experiences in childhood and the development of diabetes in adult age.

RESULTS

A sample of 52 T2DM patients (29 M, 23 F) was recruited. Mean age was 77,30±6,40 years old. A control group of 48 subjects (25 M, 22 F) was recruited as well. Mean age was 72,36±8,81 years old.

Using logistic regression, we found that the total score of TEC predicts the development of T2DM in adult age ($p=0.043$; Odds Ratio= 1.2613; 95% Confidence Interval: 1.0070-1.5797).

T2DM scored higher than HS in the questionnaire evaluating the occurrence of traumatic experiences: a history characterized by a greater number of traumatic experiences emerged in these patients.

T2DM mean score 4.80 SD 3.08. HS mean score 3.08 SD 2.13. The t-value is -2.85479. The p-value is .005531. The result is significant at $p<.05$ (Figure 1).

In particular, the items in which the greatest difference between the two groups was reported were the following:

- item 6: life threatening experience caused by an illness, a surgical operation or an accident. The t-value is 2.61117 (the p-value is .010892; the result is significant at $p<.05$);
- item 10: intense pain (the t-value is 2.71139. The p-value is .008303; the result is significant at $p<.05$);
- item 16: emotional neglect by a reference figure (the t-value is 3.31082; the p-value is .001425; the result is significant at $p<.05$.).

For what concerns the quality of childhood family relationships, a greater number of subjects belonging to the T2DM group reported an experience of maternal neglect during childhood. Moreover, a lower level of paternal empa-

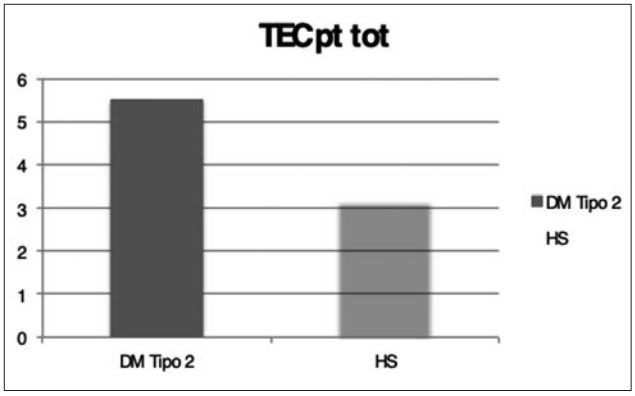

Figure 1. Traumatic Experience Checklist in both samples.

thy and a greater risk of childhood sexual abuse was also reported in this group. However neither of these data points reach a statistical significance in our sample (Figure 2).

T2DM patients have a lower resilience capacity than the control group: T2DM mean score 55.14; DS 15,7 HS: mean score 56, DS: 22.67. The t-value is -0.19777. The p-value is .843744. The result is not significant at $p<.05$.

DISCUSSION AND CONCLUSION

One of our main results, in line with the previous literature, is that patients with a diagnosis of T2DM have a higher number of traumatic experiences in their personal history when compared to the control group. Psychological trauma occurs as a result of a severely distressing event and it is often the result of an overwhelming amount of stress that exceeds one's ability to cope or integrate the emotions involved with that experience[6,9,15]. It can be noted that in a study of 30 participants with T2DM, patients with T2DM believed that their diabetes was directly linked to their perceived stress, often identified as "worry". All of the participants mentioned the interplay of worry and diabetes , citing the social context of their lives (such as tragic life events)[15].

Beyond this high level of reported stressors, the results evidenced lower levels of resiliency in our sample of T2DM patients, when compared to the control group. Based on this data we speculate that a high level of resiliency can represent a protective factor for the emergence of T2DM. Resiliency covers an important role in modulating the impact of stress on an individual.

The psychoanalytic literature, as well as the literature of other theories, recognizes a link between stress and aggressivity. Although the literature we consulted for this study often mentioned the relation of stress with hostility and anger, our study did not specifically assess the connection of stress-induced anger and aggressiveness, but it would be useful to explore the potential role of aggressivity as a mediator between stress and T2DM, in future studies. From a psychoanalytic perspective, unprocessed traumatic experiences result in an unconscious, non-integrated emotionality. These unconscious emotions have, in many cases, aggressive features: the link between trauma and non-integrated aggression is well known in psychoanalysis. Since ancient times there has been a well-established awareness about the link between anger and health; in psychosomatic medicine, in fact, hostility has always been considered a significant risk factor. Anger could be associated with T2DM through two mechanisms: unhealthy behaviors that favor obesity and activation of the sympathetic system with an excess of catecholamines responsible for an altered sensitivity to insulin and a chronic inflammatory response[16]. A review of articles from 2000-2010, presented the link between hostility, anger, and aggressiveness with health risks such as diabetes[16].

In a study conducted in the USA over 6 years, Golden and colleagues highlighted an important association between anger and the risk of developing diabetes[17]. While they did not find a relation between overall trait anger and a subsequent risk of T2DM, they did find such a link between trait anger temperament which showed a 34% increase in the risk of developing diabetes compared with those of lower levels. Also according to the authors, anger would in particular be associated to T2DM by the two different mechanisms mentioned above. While unhealthy behaviors can lead to obesity, the sympathetic system activation can consequently lead to a

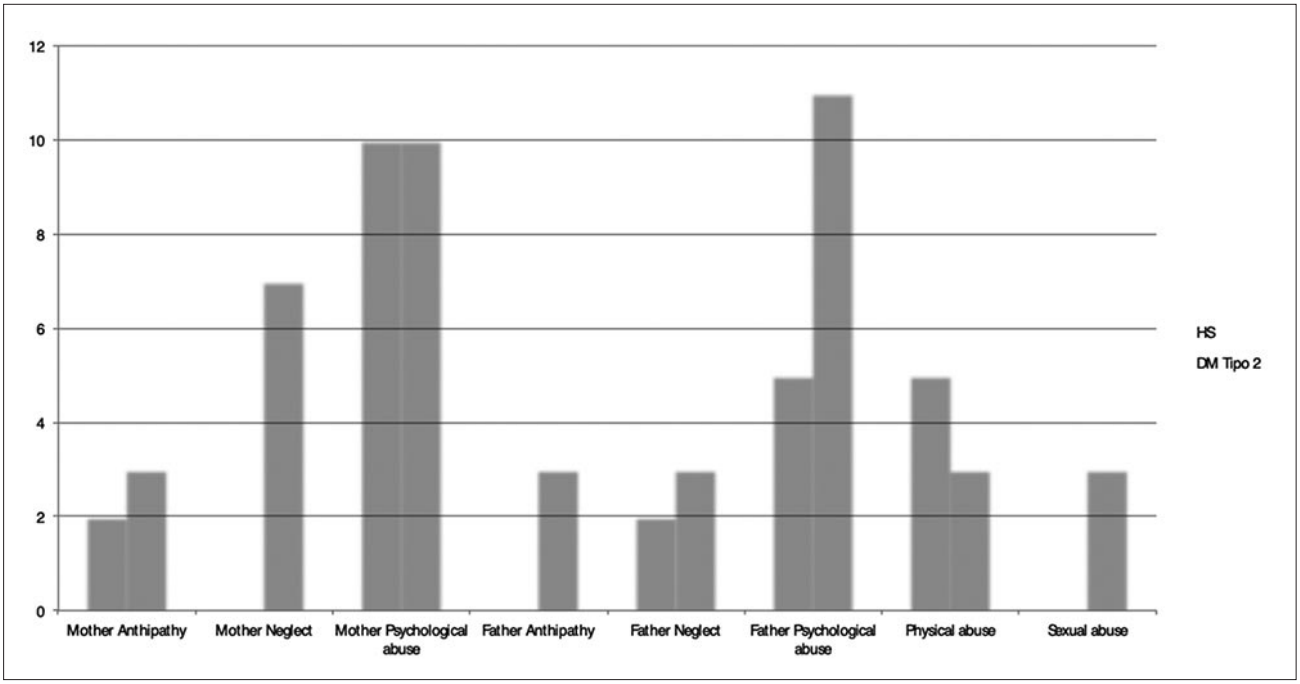

Figure 2. Childhood Experience of Care and Abuse Questionnaire in Healthy Subjects and Patients with T2DM.

higher level of catecholamines, responsible for chronic inflammatory activation, and an altered sensibility to insulin[17].

In a follow-up study which focused on the connection between anger and a predicted risk of T2DM, trait anger was assessed at baseline using the Spielberger Trait Anger Scale which is composed of two subscales: trait anger temperament and trait anger reaction. It was concluded that the participants with high trait anger at baseline had a 50% increased risk of developing T2DM and that, unlike what was found in their previous study[17], which showed an association of higher anger temperament with T2DM risk, this study instead showed a link of higher anger reaction with T2DM risk. It was posited that higher impulsivity could be connected to high anger reaction and poor self-control and aggression are associated with impaired cerebral glucose utilization. The effects of anger on unhealthy behaviors could be the link to higher risk of T2DM[18].

Relevantly, in our sample, a higher level of childhood maternal neglect combined with low resilience was reported by T2DM patients, when compared to the control group. In fact, early secure attachment and close social connections may promote physiological resilience. Maternal warmth has been found to buffer the link between low socio-economic status and metabolic syndrome and inflammation.

The instinctive human need to belong is as essential to human survival as water, food, and shelter. Therefore, child neglect is considered a form of child abuse and consists in a deficit in meeting a child's basic needs, including the failure to provide adequate health care, supervision, clothing, nutrition, housing, as well as failing to provide for their physical, emotional, social, educational and safety needs. Interestingly, a number of authors linked the experience of childhood neglect to a higher perception of loneliness in different groups[19]. As stated by a number of authors, a high perception of Perceived Social Isolation (PSI) is involved in the activation of the hypothalamic-pituitary-adrenal axis and results in the ability to reduce the gene expression responsible for regulating the modulation of glucocorticoid production, determining a condition of glucocorticoid resistance and an increased production of cortisol with a consequent alteration of glucose metabolism[19]. The negative effect of PSI is coherent with the idea that a strong social support network helps contribute to resilience. Future research could deepen the link between perception of loneliness as a mediator between childhood adversities and diabetes.

Early life adversities, such as prenatal exposure to maternal stress and parental neglect, cause negative stress reactions and impoverish resiliency. Such adversity develops neural networks predisposed to an exaggerated vulnerability to stress reactivity. In order to remain viable, cells adapt constantly to environmental cues and stressors. Some studies have found that childhood adversity such as maternal domestic violence, bullying, and maltreatment by an adult, is linked to shortened telomeres in children and adults. Shortened telomeres are linked with premature aging and weakened psychological stress resistance. Conversely, psychological stress resistance, combined with healthy lifestyle factors and good social relationships are associated with longer telomere length and can protect individuals from stress-induced telomere shortening. However, it can be noted that shortened telomere length is not just related to childhood adversity, but can in fact also be linked to stressful experiences in adulthood which contribute to disease development through emotion regulatory processes[20].

Over the past several years, psychological stress resilience, healthy lifestyle factors, and strong social connections have been associated with longer telomere length and it appears that these factors can protect individuals from stress-induced telomere shortening. This combination of factors constitutes the multisystem resilience model that is built in early life, where early exposure to severe stress, and insecure attachment, may promote neural networks primed for exaggerated vulnerability to stress reactivity, limiting development of resiliency factors. This profile of impoverished resiliency leads to rapid organismal aging and early frailty and disease. Several studies link childhood adversity to telomere shortening in children and adults. Children exposed to 2 or more traumatic stressors at age 5, such as maternal domestic violence, frequent bullying victimization and physical maltreatment by an adult, have significantly shorter telomeres at age 10 compared to children exposed to less or no violent stressors. These effects seem to extend to adulthood, as adults reporting moderate to severe childhood maltreatment and stressful experiences, such as divorce and parental separation, are more likely to have significantly shorter telomeres than those reporting no maltreatment during childhood[20].

Telomere length captures the interplay between genetics, life experiences, and psychosocial and behavioral factors. Shortened telomeres cause a tripled risk of early mortality in the healthy population. Intriguingly, there is a growing body of evidence in support of an association between short telomeres and T2DM. However, most studies have been cross-sectional in nature, precluding causal inferences: do the metabolic perturbances of T2DM cause telomere attrition, or do shorter telomeres lead to T2DM[20]? Plausible biological hypotheses support both scenarios. Further research is needed to clarify this association and to control for the existence of further possible confounding factors.

The link between the impact of stressors which are not mediated by a valid resilience and T2DM is therefore mediated by various factors which are woven together. The activation of the Hypothalamic-pituitary Adrenal (HPA) axis, particularly during neuronal development causes consequent excess of circulating cortisol, dysregulation of its diurnal profile, and the breakdown of the glucose regulatory mechanism. These are believed to lead to hyperinsulinemia and insulin resistance. Low level inflammation, in turn can lead to cytokine-induced insulin resistance. Chronic stress resulting in increased norepinephrine and cortisol could lead to depression and food cravings. Chronic stress and increasing inflammatory cytokines lead to immunological alterations. Inflammatory cytokines interfere with pancreatic B cells inducing insulin resistance and consequently T2DM. The inflammatory response of pro-inflammatory cytokines is also involved in the pathophysiology of depression. These correlations suggest that stress and inflammation promote both depression and T2DM. Epigenetic mechanisms expressed particularly through shortening telomeres, are linked to low resilience. Moreover, the adverse effect of psychological stress on health behaviors such as sedentary lifestyle, obesity, smoking, and alcohol consumption, and adherence to medication is, in the same way, reported to contribute to T2DM risk.

The data on resilience can be read in the context of

Freud's theory of mourning and melancholy[21]; of Mahler's theory on the process of separation-individuation and on the aggression of the psychology of the Self[22]. In "Mourning and Melancholy", the physiological work of mourning recognizes as a principal premise little ambivalence contained in the relationship with the lost object[21]. At the same time a low level of ambivalence would allow a successful outcome of the separation-individuation process[22]. Heinz Kohut reads aggression as a narcissistic rage caused by frustrations that are not appropriate for the phase and therefore traumatic[23]. The impossibility of the work of mourning and of the definition of separation-individuation would determine the alteration of the glucose metabolism. In this direction we find that depression increases the risk of developing T2DM[8] with a significant relationship between major depressive disorder and insulin resistance[3].

Conflict of interests: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

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