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GLYCATIVE STRESS AND SLEEP QUALITY
ITS IMPACT ON AGEING

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GLYCATIVE STRESS AND SLEEP QUALITY

Yoshikazu Yonei, Masayuki Yagi, and Wakako Takabe explain how poor quality sleep can lead to glycative stress and the onset of age-related diseases

ABSTRACT
Glycative stress is a pathophysiological condition attributed to the excessive production of reducing glucose, lipids and diverse alcohol-derived aldehydes. The aldehyde reacts with biological materials to form carbonyl proteins and/or advanced glycation end-products (AGEs), which are causes of diseases and regressive changes related to ageing. Transient spikes in blood glucose induce the production of various types of aldehyde, where the exposed aldehyde group (-CHO) of open-linear form glucose reacts with a chain-reaction behavior. Furthermore, sleep quality and glycative stress are affected bidirectionally. Research data on continuous blood glucose measurements confirmed that insufficient sleep induced a blood glucose spike. Melatonin, which is a hormone that regulates sleep quality, was shown to reduce the frequency of blood glucose spikes and to promote the degradation of AGEs. For the prevention of diseases related to glycative stress and health promotion, countermeasures must be taken to retain and restore sleep quality.

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KEYWORDS
Glycative stress, sleep quality, melatonin, aldehyde spark, glucose spike

THERE IS A DIVERSE VARIETY OF symptoms and processes related to ageing. Vascular ageing, bone ageing, muscle ageing, and neural ageing induce, respectively, arteriosclerosis, osteoporosis, sarcopenia, and Alzheimer's disease. Additionally, there are also a diverse variety of risk factors related to the onset of ageing, resulting in individuals experiencing different ageing processes. These symptoms begin and progress gradually through the thirties and forties and can often lead to diseases. However, a symptom is designated as a disease only when it is diagnosed as a disease based on a diagnostic criteria. It would be much more worthwhile to find signs of symptoms in the early stages of life, such as in the thirties or forties, to delay progression and prevent the onset of disease than to begin medical treatments after the diagnosis has been made.

Medical institutions practising anti-ageing treatments recommend examinations to assess the degree of ageing and related risk factors[1-3]. The degree of ageing evaluations consist of categories including the functional ages in vascular, neural, hormone, muscle, and bone age. Assessment of the risk factors of ageing consist of mental, oxidative, glycative, immune stress and lifestyle categories. Among the major risk factors against arteriosclerosis, smoking is assessed as an oxidative stress and diabetes and lipid abnormality are assessed as a glycative stress. When a weak point in ageing is discovered, which is an item evaluated as being at the most advanced age, and is left without any countermeasures, other functional elements are adversely affected. Neglecting treatment for the most significant risk worsens other risks (a multiplier effect). Improving the weak function and reducing the most significant risk factor is an appropriate overall balance that must be maintained.

Glycative stress

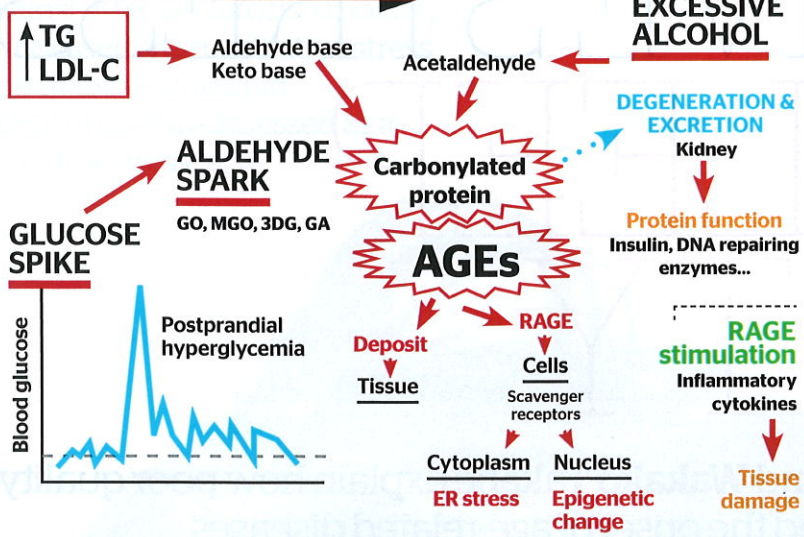
Glycative stress is a pathophysiological condition attributed to the excessive production of reducing sugars (glucose), lipids and diverse alcohol-derived aldehydes. The aldehyde reacts with biological materials to form carbonyl protein and/or advanced glycation end products (AGEs). AGEs/RAGE signalling is stimulated, and a variety of changes occur, which are causes of diseases or regressive changes related to ageing (*Figure 1*)[4-6].

Causes of glycative stress are the following:

- Blood glucose spikes
- Lipid abnormalities, such as high triglyceride level and high LDL cholesterol level
- Excessive alcohol consumption.

A material common in these three causes is aldehyde. There are some people who do not have an abnormal fasting blood glucose level but have a blood glucose level of 160 mg/dL or higher after meals, which is referred to as a 'blood glucose spike.' Recent research has clarified that this postprandial hyperglycaemia induces the rapid ▷

Figure 1 Concept of glycative stress



The glucose spike evokes aldehyde sparks. The trigger is an open-linear form glucose with exposed aldehyde-base (-CHO) at the spike peak, followed by a chain-reaction to free saccharide and/or sugar-chains on the surfaces of proteins and cells (authors' hypothesis). Triglyceride (TG); low-density lipoprotein-cholesterol (LDL-C); advanced glycation end products (AGEs); receptor for AGEs (RAGE); glyoxal (GO); methylglyoxal (MGO); 3-deoxyglucosone (3DG); glyceraldehyde (GA); endoplasmic reticulum (ER)

▷ progression of arteriosclerosis and a diverse variety of physical damage. The glucose spike evokes an 'aldehyde spark.' Various types of aldehyde are simultaneously formed with a chain-reaction[7]. Glyceraldehyde (GA), glycolaldehyde, acetaldehyde (AA), 3-deoxyglucosone (3DG), glyoxal (GO), methylglyoxal (MGO) and malondialdehyde are representative aldehydes (*Figure 2*). The aldehyde group (-CHO) is a highly reactive compound, and enzymes for reactions are not necessary. Processes of reactions are regulated by substrate concentration, temperature, and time.

Sugars in glucose spikes are usually saccharides with a cyclical form. A portion of the glucose molecule is decyclized to present an open-linear form. The aldehyde group (-CHO) is exposed and exerts harmful effects.

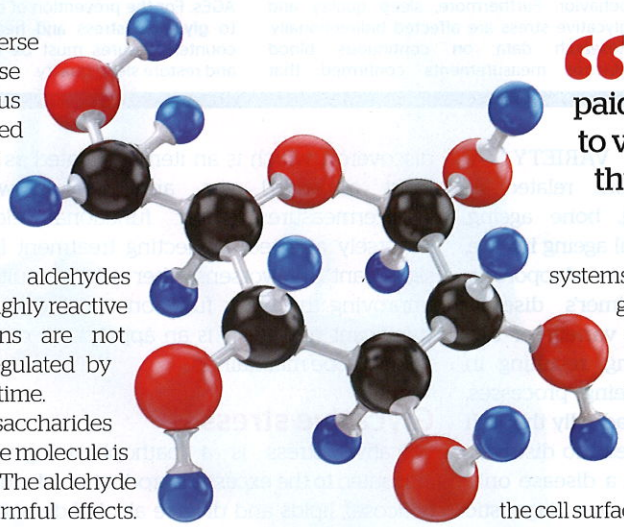


Figure 2 Intermediate aldehydes generated by the glucose spike

Glucose (open-linear form)	3DG	Glycel-aldehyde (GA)	Glycol-aldehyde	Acet-aldehyde	Glyoxal (GO)	Methyl-glyoxal (MGO)
CHO CHOH CHOH CHOH CHOH CH_2OH	CHO C=H CH_2 CHOH CHOH CH_2OH	CHO CHOH CH_2OH	CHO CH_2OH	CHO CH_3	CHO CHO	CHO C=O CH_3

However, the rate of ring-opening (i.e. change to open-linear from) is as small as 0.002%, and the adverse effect called glucotoxicity is subdued. Thus, we hypothesised that glucose spikes produce a variety of aldehydes with a chain-reaction. Where the exposed aldehyde-base is in the open-linear form glucose reacts with carbohydrate chains on protein surfaces or free saccharides (i.e. glucose, fructose, pentose) in blood and tissue fluid.

Recently, attention has been paid to glucose spikes in relation to vascular endothelial damage, thus facing an increased risk of cardiovascular events. The reason, however, remains unclear. These 'aldehyde sparks' reactions surely play a significant role in the pathogenesis of tissue damage, i.e. endothelial dysfunction, since aldehydes are highly reactive with protein. We shouldn't take glucose spikes lightly as merely postprandial hyperglycaemia.

Glycative stress and diseases related to ageing

Humans have an anti-oxidative stress system inside the body, and we have struggled with oxidative stress for several hundred thousand years. However, it was only several decades ago that glycative stress became a threat to the general population, due in part to changes in our diet and reduction in physical activity. Thus, the physical

"Recently, attention has been paid to glucose spikes in relation to vascular endothelial damage, thus facing an increased risk of cardiovascular events."

systems of humans are extremely vulnerable to glycative stress. Diseases strongly related to glycative stress, such as obesity, diabetes mellitus, and dyslipidemia have been increasing in number.

AGEs are formed due to glycative stress and affect cells and tissues. AGEs are uptaken via scavenger receptors on the cell surface (a receptor participating in the removal of waste materials such as denatured protein). Consequently, endoplasmic reticulum (ER), which is an organelle in cells, is under stress[4,6]. This stress is called ER stress, which leads to the impoverishment of cells. AGEs bind with a receptor called RAGE (receptor for AGEs) on cell surfaces, and cells produce inflammatory cytokine, which induces inflammation in peripheral tissues. TNF-α, IL-1, IL-6 and MCP-1 are cytokines produced through AGEs/RAGE signalling.

Glycation of skin collagen leads to taut skin and yellowish discolouration. Glycation of bone collagen results in fragile bones more prone to fractures[8,9]. Alzheimer's disease is pathogenetically associated with the glycation of an accumulated protein named β-amyloid in the brain, where the toxicity of β-amyloid is increased, inflammation occurs in peripheral brain cells

and symptoms develop[10]. Cataracts are induced by the glycation of crystallin protein, which comprises the crystalline lens[11]. Glycation also affects the ovaries and testicles to be an attributing cause of infertility in females and males[12].

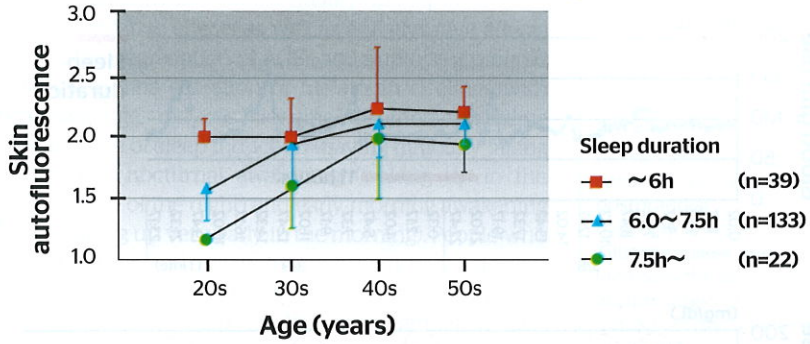
These disorders are only a very small sample. Glycative stress is related to a diverse variety of causes for the onset and progression of many diseases related to ageing.

Quality of sleep and glycative stress

Approximately 40% of patients with diabetes, which is strongly linked to glycative stress, have disease complications related to sleep disorders. Sleep apnea syndrome (SAS), which is a major disease resulting in the decline in sleep quality, is frequently associated with complications related to obesity and diabetes[13]. That is to say, there is a bidirectional correlation between sleep and carbohydrate metabolism. To reduce glycative stress, prevention and treatments for carbohydrate disorders and sleep disorders must be performed simultaneously.

Prior research revealed skin autofluorescence (AF), which shows an intensity of AGE-derived fluorescence, is affected by the length of sleep and can therefore be used as a glycative stress marker. In the graphic chart of the level of skin AF by age, the AF value curve with ageing was higher and shifts upwards for persons with a shorter duration of sleep when compared to persons with a longer duration of sleep (*Figure 3*)[14]. In short, the people with a shorter duration of sleep had a large amount of AGEs accumulated in the skin, while the people with a longer sleep time showed reduced glycative stress.

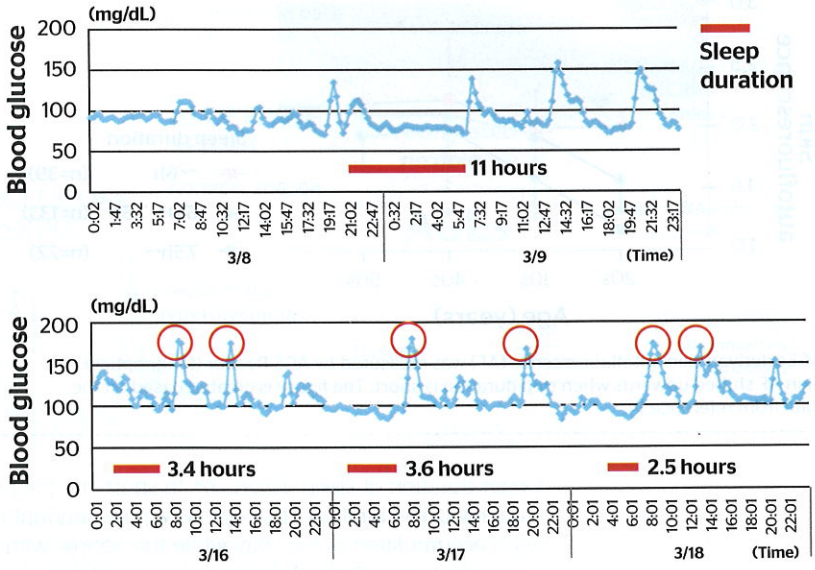
Figure 3 Changes of skin autofluorescence with ageing



AGEs derived skin autofluorescence (AF) was measured by AGE Reader (Diagnoptics). Skin AF shifted upwards when slep duration is short. The figure is created based on the data from reference 14.

We analysed the association between sleep quality and changes in blood glucose level, using continuous glucose level monitoring. One of the results is shown in *Figure 4*. In this case, when the subject had sufficient sleep, ▷

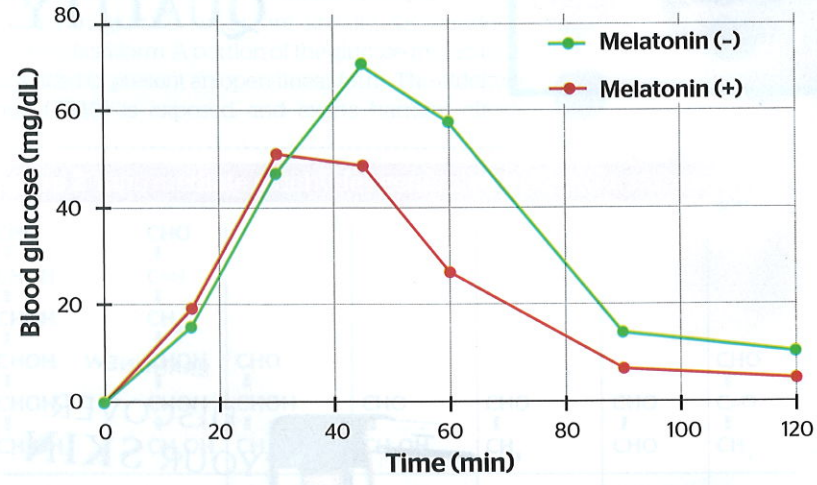
Figure 4 Correlation between glucose spikes and duration of sleep



Subject: 25 year old male. Glucose spikes are marked when the time of sleeping is short. The blood glucose levels were monitored by Free Style Libre (Abbott).

> To delay the absorption of causative substances, it is recommended to eat slowly, chewing well, eat vegetables first, which are high in fibre, and intake vinegar, black vinegar or yoghurt before starting a meal. Contrarily, it is not recommended to eat staple foods alone (eating only cooked white rice or bread).

Figure 5 Postprandial glucose change after intake of steamed rice (200 g) at breakfast



Subject: 22 years old female. Melatonin (+): 2 mg melatonin was orally administered at the previous night (21:00pm). Melatonin (–): without melatonin administration. The figure is created based on the data from reference 19.

▷ postprandial blood glucose level elevated mildly, not reaching 160 mg/mL in the next morning. However, it was shown that, when the subject slept for only 3 or 4 hours, the peak blood glucose level drastically increased after breakfast. Insufficient sleep is likely to induce blood glucose spikes.

Effects of melatonin

One of the reasons that the quality of sleep declines with increasing age is the decrease in the secretion of melatonin. Melatonin is a hormone that is secreted by the pineal gland and plays an important role in regulating the sleep-wake rhythm to transmit the time information to the whole body[15]. Melatonin has powerful anti-oxidative effects, and recent studies have revealed that melatonin has effects on the reduction of glycative stress. Examinations of melatonin *in vitro* showed that melatonin had no inhibitory effect on AGE formation[16], and no control effects on AGEs/RAGE signalling[17]. However, melatonin was shown to promote AGE degradation by cleaving α-diketone structures[18].

Figure 5 shows one of our examination results on melatonin intake. Postprandial glucose change after breakfast was subdued in the case of melatonin administration at bedtime on the day prior to the measurement[19]. It was observed that high-quality sleep with ample secretion of melatonin could reduce the glucose spikes.

The mechanisms of melatonin effects to improve carbohydrate metabolism disorders are assumed to be as follows:

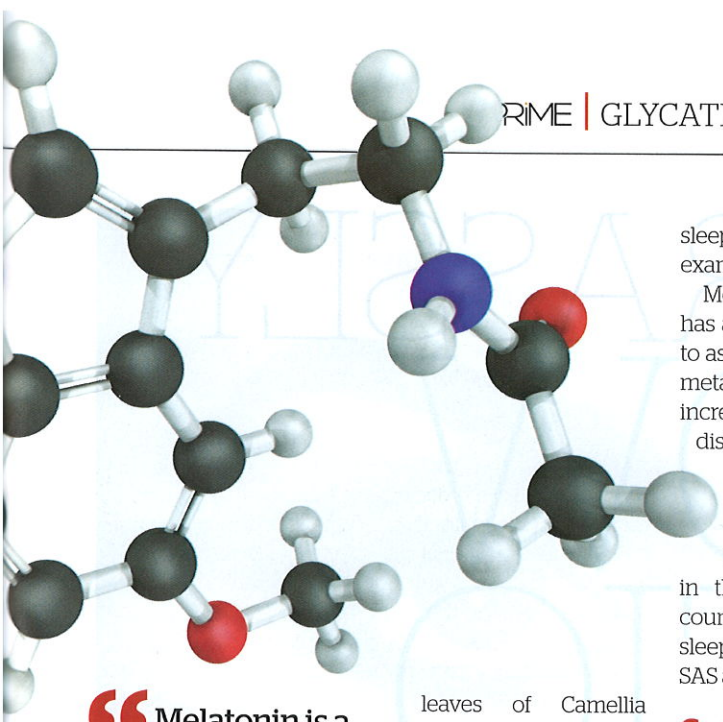
- To reduce the secretion of glucocorticoid, such as cortisol, from the adrenal cortex
- To restore the vibration of orexin
- To reduce ER stress of pancreatic β-cells and restore insulin secretion[19].

Countermeasures against glycative stress and improvement of sleep quality

Countermeasures against glycative stress are classified into four groups according to the four stages of the glycation reaction, as follows:

- To delay the absorption of causative substances, such as carbohydrates and fat
- To inhibit the formation of AGEs
- To promote the degradation and excretion of AGEs
- To control AGEs/RAGE signalling[5].

To delay the absorption of causative substances, it is recommended to eat slowly, chewing well, eat vegetables first, which are high in fibre, and intake vinegar, black vinegar or yoghurt before starting a meal. Contrarily, it is not recommended to eat staple foods alone (eating only cooked white rice or bread). Instead, eating gyudon, a bowl of rice topped with beef; mabodon, a bowl of rice topped with mabo tofu or curry and rice can help lower postprandial hyperglycaemia. To inhibit the formation of AGEs, it is important to drink liquids containing many anti-glycative functional ingredients such as tea (made from



> "Melatonin is a hormone that is secreted by the pineal gland and plays an important role in regulating the sleep-wake rhythm to transmit the time information to the whole body."

without exception. Therefore, elevating the quality of sleep plays a crucial role as a countermeasure for glycative stress. To name methods to enhance the quality of sleep, the improvement of the sleeping environment, melatonin replacement and management of mental and physical stress are essential. In addition, comfortable bedding does not only provide sound sleep but also could provide an improvement in glycolipid metabolism. Our study has suggested that the usage of mats with a distinctive 4-layer 3-dimensional structure improves both the quality of sleep and glycolipid metabolism (however note that this examination was an open-label uncontrolled trial)[24,25].

Melatonin is involved in the quality of sleep. Melatonin has anti-oxidative effects as well as anti-glycative effects to assist the degradation of AGEs and improve glycolipid metabolism. The secretion of melatonin declines with increasing age, induces sleeping disorders including disturbance of sleep induction (having difficulty falling asleep), nocturnal awakening (waking up in the middle of the night) and early morning awakening (waking up very early in the morning). People who have glycolipid metabolism disorders with a decline in the quality of sleep are recommended to take countermeasures, such as the arrangement of the sleeping environment in bedding, medical treatment for SAS and melatonin intake.

Conclusion

The quality of sleep and glycative stress, which is a risk factor for ageing, are affected bidirectionally. The decline in the quality of sleep evokes blood glucose spikes, and subsequently, an aldehyde spark. Further studies are awaited to clarify the mechanisms of sleep quality decline and to establish countermeasures contributing to the prevention for the onset and progression of diabetic complications and age-related diseases due to glycative stress.

▶ ***Declaration of interest*** *The authors claim no conflict of interest in this study.*

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▶ ***Figures 1-5*** *Data © Professor Yonei*

Key points

- The sleep quality affects glucose metabolism and less quality increases the glycative stress
- The sleep shortage causes day-time postprandial hyperglycemia, i.e. 'Glucose spikes' and increases the skin accumulation of AGEs (advanced glycation end products).
- Melatonin is a hormone communicating between the sleep quality and glycative stress
- Melatonin contributes to cleavage of AGEs and reduces the day-time glucose spikes
- In the glucose spike reaction, the exposed aldehyde-group of the linear form glucose evokes the chain-reactive formation of aldehydes, i.e. 'Aldehyde sparks', thus causing tissue protein damage

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