

Periodontal Disease And Its Impact on Health, From Cardiovascular Diseases to Metabolic Syndrome

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Abstract: As the life expectancy of the population increases, we are increasingly confronted with chronic diseases. Periodontal disease and chronic inflammatory diseases have in common the development of an inflammatory response. Recently, studies have shown that there is an increasingly clear link between the inflammatory mechanisms of periodontal disease and those of chronic inflammatory diseases such as diabetes, atherosclerosis, cardiovascular problems, and so on. The aim of this work is to present the results of the most recent studies on the bi-directional relationship between periodontitis and some chronic systemic diseases: cardiovascular risk, coronaropathy, atherosclerosis, obesity, diabetes and metabolic syndrome. To do so, we carried out a bibliographic review based on 29 articles, 2 books and a web page. The articles were searched on the PUBMED database, and 23 of them were published after 2012.

Periodontal disease, through complex chain reaction mechanisms, has an impact not only on oral health, but also on the overall health of the host. It is an important cardiovascular and inflammatory risk factor. A periodontitis, if diagnosed and treated in time, may not involve so much morbidity. Studies of periodontal disease are increasing in number and tend to show increasing links with other diseases, such as respiratory diseases, renal diseases and pregnancy accidents.

Keywords: Periodontal disease, cardiovascular disease, systemic disease, diabetes, metabolic syndrome.

I. Introduction

Many systemic diseases manifest themselves in the gums, producing signs and symptoms that recall gingivitis and periodontitis [1]. Periodontitis is a chronic infection and inflammatory disease of the periodontal tissues and adjacent structures [2]. This disease affects 64% of the US senior population [3]. This chronic infection has several risk factors:

- Modifiable: microorganisms, tobacco, diabetes mellitus, cardiovascular diseases, drugs, stress and obesity.
- Non-modifiable: osteoporosis, hematic problems, host response, hormonal alterations in women, and pregnancy [4].

There is growing evidence that periodontal disease is a risk factor for the development of cardiovascular disease: atherosclerosis, aneurysms, valvular disease, carotid dissection [5], and type II diabetes, respiratory diseases, kidney diseases, and problems during pregnancy [2]. Periodontitis and cardiovascular disease present the same risk factors: stress, tobacco, age and genetic predisposition [6, 7].

The purpose of this work is to expose the inflammatory mechanisms that link periodontal disease and systemic impairment. We will start with simple inflammatory mechanisms related to cardiovascular diseases, and then we will develop these mechanisms in connection with other pathologies such as atherosclerosis, obesity, diabetes, and finally the metabolic syndrome.

II. Material and methods

To carry out this work, we began by looking for articles on post-2012 PUBMED with the following keywords: periodontal disease, cardiovascular disease; Then periodontal disease, systemic disease; Periodontal disease, diabetes; Then metabolic syndrome and periodontal disease. Only English articles were considered. The main exclusion criteria are the animal and / or in vitro study and articles earlier to 2012 in the first research. This search resulted in a total of 623, 593, 684, and 68 articles, respectively. Subsequently, we selected the articles according to the title and the abstract. We arrived at a total of 23 articles. Finally, we have selected some

of the articles mentioned in the bibliography of some previously found articles that appeared important, although they were published before 2012. We also chose to use two books and one website. We have reached a total of 30 references.

III. Results

Foreword: mechanisms related to inflammation

The inflammatory reaction begins with a chemical "warning" triggered by a considerable discharge of chemicals into the interstitial fluid. The macrophagocytes carry membrane receptors called TLR receptors ("toll receptors"), which play a key role in the downgrading of the immune response. Activation of TLR receptors causes the release of chemicals called cytokines that feed inflammation and attract leukocytes [8].

The subgingival microbiota in the case of periodontitis imposes a persistent presence of gram-negative bacteria on the host. These bacteria and their toxic secretions, such as lipopolysaccharides (LPS), produce cytokines by macrophages (IL-1 α , 1 β and TNF- α). In the case of periodontitis, the present bacteria have access to Periodontal tissues and systemic circulation through the epithelium of the damaged gum tissue, giving the necessary impulse to systemic inflammation and infection [9].

Cardiovascular risks

Cardiovascular diseases account for 40% of deaths and are the leading cause of death in industrialized countries. The main factor in these diseases is atherosclerosis [10]. In 2005, Desvarieux et al collected dental plaque samples and measured the diameter of their carotid arteries in parallel by imaging. They demonstrated a correlation between a high dental bacterial level and a fine carotid diameter, independent of C-reactive protein levels [11]. A study in 2014 by Yu et al. [7] examined the relationship between prevalence and incidence of periodontal disease and the first cardiovascular event in a group of 39,863 American women followed for 15.7 years average (*Fig. 1*). It was found that women with periodontal disease were more often overweight or obese, and had total cholesterol, as well as higher LDL, triglyceride and hsCRP. In addition, compared with women without periodontal disease, cardiovascular events in women with periodontal disease were more frequent (prevalence of 1.27 and incidence of 1.40). The authors concluded that the incidence and prevalence of periodontal disease implies a higher risk of developing a future myocardial infarction, ischemic stroke and vascular problems [7].

Coronaropathy

Coronary artery disease is a disease of myocardial arteries. They result in myocardial ischemia, which manifests as an angina pectoris, or as a myocardial infarction. In recent decades, oral health has become an area of interest in the prevention and investigation of risk factors for cardiovascular disease [10]. Vedin et al (2014) conducted a statistical study linking risk factors to cardiovascular disease in a population with chronic coronary artery disease, and the number of teeth and bleeding gums in this population [10]. Their conclusion is that poor oral hygiene, characterized by loss of teeth and bleeding gums, is associated with an increased risk of cardiovascular disease. Ramirez JH et al, in 2014, conducted a study of 44 patients, half with moderate or severe periodontitis, and showed that patients with periodontitis had higher levels of E-selectin, MPO (Myeloperoxidase) and ICAM -1 (Intercellular Adhesion molecules 1). These inflammatory proteins are associated with endothelial dysfunction, development of atheroma plaques, systemic inflammation and cardiovascular events [11]. The risk of ischemic heart attack (and not haemorrhagic) is higher in people with periodontitis. In a study by Lafon et al., gingivitis did not demonstrate the same effects. Loss of teeth, considered the last stage of periodontitis, is also considered a risk factor for heart attacks [12]. According to Lafon et al, periodontitis is associated with an increase in C-reactive protein, which is itself involved in atherosclerosis and the incidence of myocardial infarction.

Atherosclerosis

One of the main factors contributing to cardiovascular and cerebrovascular diseases is atherosclerosis [13]. Among the characteristics of these diseases is the accumulation of cholesterol in the epithelium of the arteries which causes their narrowness. Periodontal disease and atherosclerosis are associated with the same risk factors such as tobacco and obesity. They are both multi-factorial. The initial observation that atherosclerosis is more frequent in subjects with periodontitis dates back to more than 10 years ago. It seems that the links between these two pathologies could be explained by common risk behaviours in subjects such as obesity or smoking. Thus, the associations observed between one of these diseases are difficult to explain [14].

The AHA (American Heart Association) conducted a bibliographic review to try to explain several plausible mechanisms that would link periodontal disease and atherosclerosis. Several mechanisms have been discussed, the first being systemic inflammation caused by pathogens present in periodontal disease. This was demonstrated by high levels of C-reactive protein, tumour necrosis factor α (TNF- α) and interleukin 6 [15]. The

initial hypothesis of AHA in this study was that periodontal disease and cardiovascular disease were associated independently. This relationship has been demonstrated with an A level of evidence. With no evidence that periodontitis treatment would decrease cardiovascular disease, the AHA concluded that periodontitis can not be retained as a cause of cardiovascular disease. These mechanisms explained we can affirm that although periodontitis does not cause cardiovascular disease, it must be treated in the interest of not worsening a pre-existing arteriosclerotic vascular disease [15]. To conclude, periodontitis although independently related to cardiovascular disease, is recognized as a contributing cause or an aggravating factor to atherosclerosis [15] (Fig. 2).

Obesity

A person is considered overweight if his or her BMI is between 25 and 30 kg/m². However, only waist circumference could be an accurate indicator of the distribution of abdominal fat and related to health problems [16]. The probability of having a periodontitis in an obese subject increases by 30% compared with a healthy subject, with more loss of clinical attachment in obese patients and a higher BMI in subjects with periodontitis [16, 17]. In France, the study by Benguigui et al in 2012, comprising 186 individuals, shows that the number of sites with a plaque index greater than 2 is significantly related to obesity.

Oxidative stress and inflammatory response:

Obesity is characterized by excessive fat deposition in the adipose tissue resulting in increased oxidative stress leading not only to endothelial dysfunction but also to negative effects on periodontal tissues due to increased cytokines Pro inflammatory.

Genetic modulation in obesity and periodontics

Specific genetic polymorphisms have been associated with susceptibility to weight gain. The expression of these susceptibility genes can be influenced by epigenetic and environmental factors. Recently, some microRNAs (miRNAs) have been identified and are potentially susceptible to act on inflammatory processes [16].

Link between obesity and periodontal bacterial flora:

Obesity can interfere with the ability of the immune system to respond appropriately to an infection induced in animals by one of the major periodontal pathogens, *Porphyromonas gingivalis* [16].

Zeigler et al analyzed the flora of subgingival biofilms in adolescents in a cross-sectional study. Twenty-three bacterial species, including *P. gingivalis*, *A. actinomycetemcomitans* and *P. micra*, were three times more present in obese subjects compared to controls of normal weight. Some germs, such as Proteobacteria, *Campylobacter rectus* and *Neisseria*, were present in six-fold higher amounts in obese subjects [16].

This finding is consistent with other recent clinical findings that demonstrate that the number of teeth with periodontal pockets greater than or equal to 4 mm has been statistically associated with obesity in adult subjects [16]. According to these information, obesity exacerbates the inflammatory mechanisms caused by periodontitis and vice versa.

Diabetes

Diabetes is a metabolic disease characterized by an increase in glucose level. Inflammation is the main characteristic of periodontitis and MD (Diabetes Mellitus). DM1 and DM2 are both associated with an increase in bio markers of inflammation, which leads to macro and micro vascular complications [18].

Effects of DM on periodontitis:

In 1990, Shlossman et al demonstrated an increase in the prevalence of periodontitis in patients with DM2 [19]. Control of blood glucose directly influences the increased risk of periodontal disease. It has also been shown that in well-controlled DM, with HbA1c at 53mmol/mol or less, diabetes has no effect on periodontitis. On the other hand, the risk of periodontitis increases exponentially as glycaemic control deteriorates. In addition, calcium channel blockers prescribed to control high blood pressure in diabetics cause gingival growths, which complicates oral hygiene in patients and increases the risk of bacterial accumulation in periodontal pockets [20].

Effects of periodontitis on DM:

In 1996, Taylor et al demonstrated that an already established and advanced periodontitis increases the chances of loss of glycaemic control by six [21]. Also, a study on changes in HbA1 levels in subjects without diabetes but with periodontitis showed that over 5 years, non-diabetic subjects saw their HbA1c multiplied by 5

compared to subjects without diabetes and without periodontitis. This study therefore suggests that periodontitis alone could trigger a pre-diabetes in a healthy subject at first [22]. The correlation between periodontitis and DM2 is thus bidirectional. Studies have also demonstrated the link between the severity of periodontitis and the complications of DM2. Moderate to severe periodontitis was associated with an increase in macroalbuminuria, final stage kidney disease, atherosclerotic plaque calcification, carotid intimal thickening and cardio-renal mortality [18]. Insulin resistance and inflammation have been studied as causal mechanisms leading to the association between diabetes and periodontitis, but dyslipidaemia may also play a role. Hyperglycaemia negatively influences the regulation of the host's inflammatory response via the deposition of intrinsic glucose products in the tissues, including the periodontium, and thus stimulates pro-inflammatory cytokines [23].

Metabolic Syndrome

Metabolic syndrome, also known as Reaven's syndrome, insulin resistance syndrome, plurimetabolic syndrome, syndrome X or the lethal quartet [9], is characterized by at least 3 of the following physiological and physical changes: abdominal obesity Hypertension (systolic pressure > 135mmH or diastolic pressure > 85mmHg) and poor glucose tolerance, or even hyperglycaemia ($\geq 100\text{mg / dl}$) or hypertension ($> 100\text{mg / dL}$ Treatment for diabetes) [3, 24.] It is associated with a strong predisposition for diabetes and cardiovascular problems [25, 26]. This syndrome is a putative risk factor for cardiovascular disease. Studies show that the mechanisms causing an aggravation of the metabolic syndrome in subjects with periodontitis and vice versa are the same mechanisms of inflammation described in obese and diabetic people.

Impact of Periodontal Disease on Metabolic Syndrome:

According to Gomes-Filho et al and Nibali et al, there is a relationship between severe periodontitis and metabolic syndrome [27, 28, 29]. According to Gomes-Filho et al, severe periodontitis may predispose individuals to the metabolic syndrome by mechanisms of passage of pathogenic bacteria initially in the oral cavity to the bloodstream and thus cause a general inflammation that exacerbates the metabolic syndrome. However, this same study shows the absence of a relationship between the metabolic syndrome and mild to moderate periodontitis [24].

Impact of Metabolic Syndrome on Periodontal Disease:

According to Morita et al, patients with periodontal pockets greater than or equal to 4 mm have a 40% greater chance of having a metabolic syndrome within 4 years [26]. Some studies have shown that treating periodontitis in patients with metabolic syndrome results in a reduction in the systemic level of C-reactive protein, triglycerides, leukocytes and an increase in HDL [28, 29]. According to a study by Shimana et al, non-surgical treatment of periodontitis results in a 1/3 reduction in the amount of markers of inflammation [29]. These results show that there is a bi-directional correlation between the metabolic syndrome and periodontitis.

IV. Discussion

All the research we did about the link between periodontitis and systemic diseases agreed that there is a correlation between the two. Some of them are cautious and only admit a plausible link; others are more categorical and affirmed the existence of a bi-directional relation between the two. The AHA concluded that periodontitis can not be retained as a cause of cardiovascular disease, however, from a clinical point of view, there is a significant difference between a relationship and a cause. The literature agrees that patients and the medical community should be informed that a controlled and controlled periodontal disease can prevent the progression of diseases induced by atherosclerosis [14; 15]. Since ADA's affirmation of the independent relationship between periodontitis and atherosclerosis, new studies have been carried out asserting that periodontal disease, caused by high-risk pathogens, Aa, Pg, Tf, Td, or Fn, can increase Pathogenesis of atherosclerosis. According to our findings, there is a bi directional relation between obesity and periodontal disease; obesity increasing the inflammation mechanisms produced by periodontitis and vice versa. This leads to systemic inflammation that is more rapidly achieved in the absence of treatment. These mechanisms are summarized in *Fig. 3*.

AS for diabetes, all the studies mentioned earlier tend to show that periodontal disease, through the various mechanisms previously explained, has an impact on the systemic inflammation of the organism. The results show that there is a bi-directional relation between the metabolic syndrome and periodontitis. Metabolic syndrome is an indicator of tooth loss and aggravation of periodontal disease. The diagnosis of periodontitis should be part of the diagnosis of the metabolic syndrome and that its treatment should be an integral part of the treatment of the metabolic syndrome. However, the association between metabolic syndrome and periodontitis is not so noticeable in that cardiovascular disease risk factors, which include metabolic syndrome, are associated with periodontitis [17, 26]. In *Fig. 4*, we can observe the various correlations that exist between periodontal disease, systemic inflammation, obesity, diabetes, atherosclerosis and finally metabolic syndrome. We see how

we move from a simple periodontitis to something much more global: the metabolic syndrome. It is important to note that not all periodontal tissue studies have the same diagnostic criteria. Some simply use the CPI, as indicated by the WHO, and others use their own criteria [25]. Similarly, with the pathologies described such as the metabolic syndrome [17].

In 2007, WHO recognized the link between oral health, health and quality of life. It has been suggested that oral health is an area that is all too often neglected when looking at the overall health of an individual. Periodontitis and diabetes as well as other systemic diseases are now considered to be associated. Some scientists speak of a "silent" epidemic of the oral cavity and teeth [30]. This is why in our opinion, it is necessary to intensify the communication between dentists and doctors in the interest of treating the patients in their globality.

V. Figures and tables

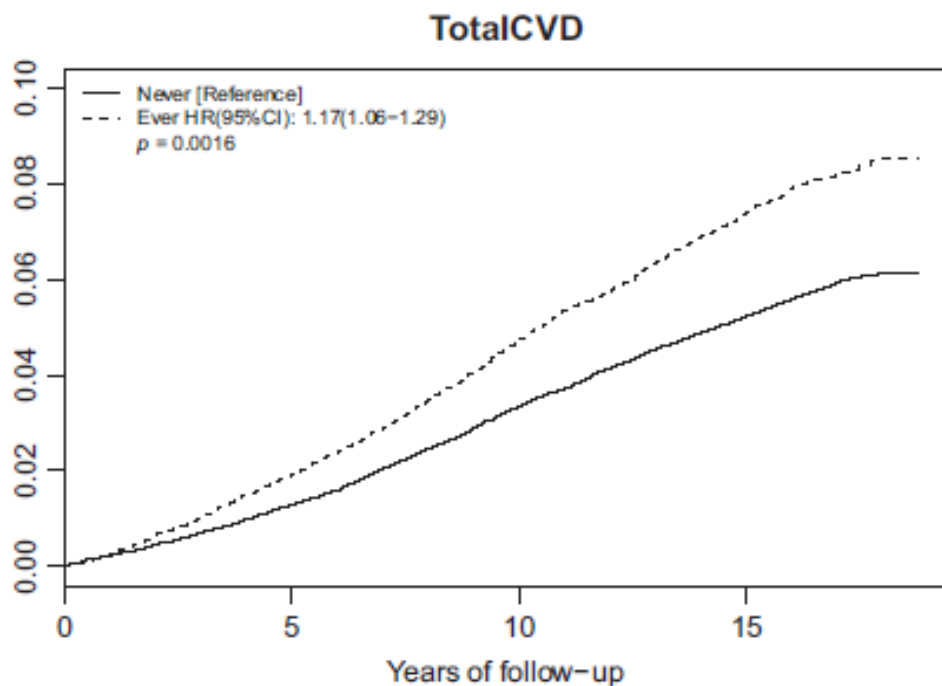


Figure 1. Curves showing the incidence of cardiovascular events in women with periodontal disease (dotted lines) in women without periodontal disease over the years [7].

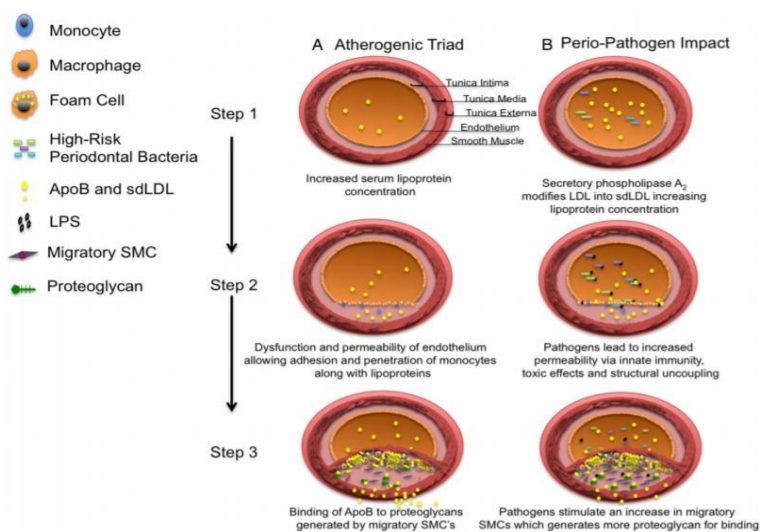


Figure 2. Atherogenic triad in the presence and absence of high risk periodontal pathogens. Column A: Atherogenic Triad. Column B: Atherogenic Triad in the Presence of Periodontal Bacteria [15].

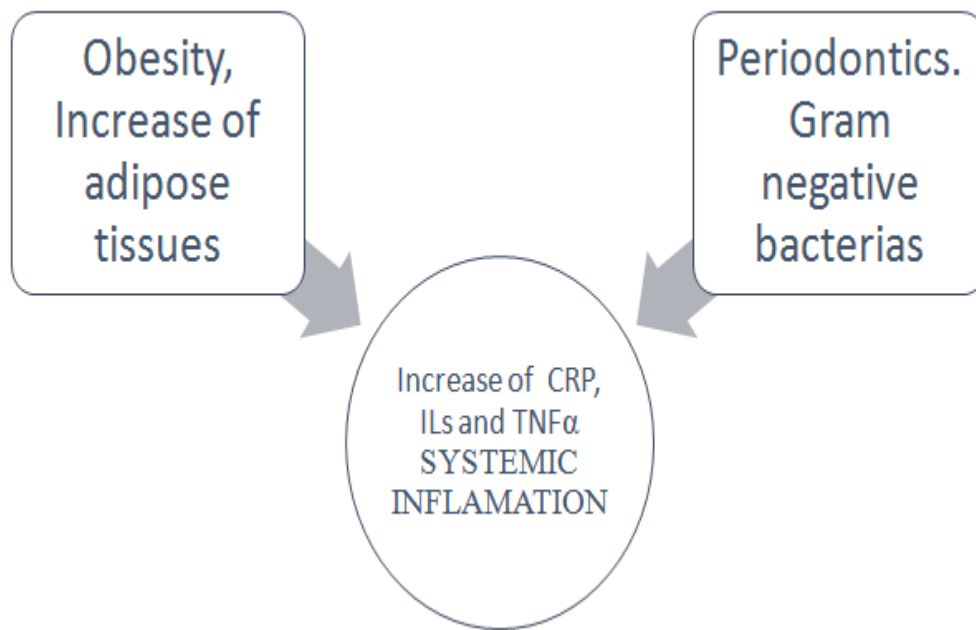


Figure 3. The combination of obesity and periodontal disease exacerbates the mechanisms of inflammation.

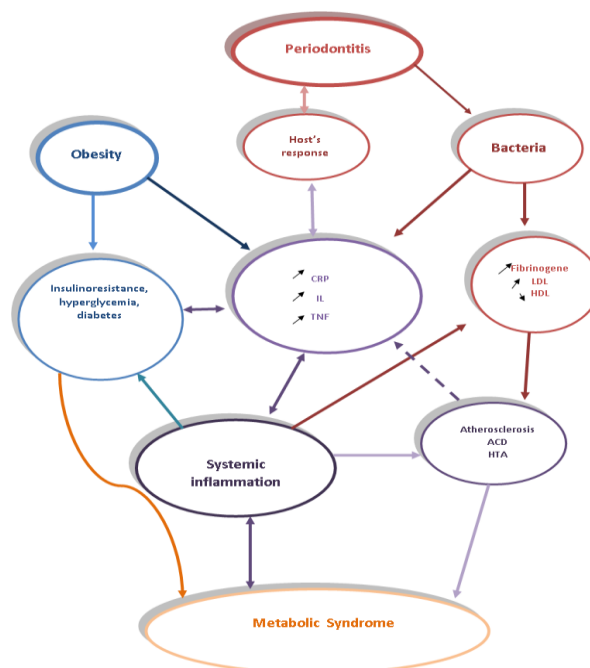


Figure 4.Correlations between periodontal disease, systemic inflammation, obesity, diabetes, atherosclerosis and finally the metabolic syndrome.

VI. Conclusions

- Patients with periodontal disease and/or low dental hygiene are more likely to be exposed to cardiovascular events.
- Moderate or severe periodontitis involves endothelial dysfunction, increased prevalence of atheroma plaques and cardiovascular events.
- There is an association between moderate and severe chronic periodontitis, with *P. gingivalis* and *P. intermedia*, and systemic inflammation.
- Untreated periodontal disease causes systemic inflammation through the passage of gram-negative abscesses into the bloodstream.
- Periodontitis does not cause cardiovascular disease, but is an aggravating factor.

- Obesity and DM exacerbates the inflammatory mechanisms caused by periodontitis and vice versa, leading, in the absence of treatment, to systemic inflammation achieved more rapidly.
- Periodontitis, as a chronic inflammatory process, could have adverse effects on the metabolic syndrome.
- Surfacing treatment of periodontitis involves a significant decrease in PCR in the body, and non-surgical treatment of periodontitis in a subject with metabolic syndrome involves a significant decrease in inflammation markers.

We have shown that periodontal disease, through complex chain reaction mechanisms, has an impact not only on oral health, but also on the overall health of the host. It is an important cardiovascular and inflammatory risk factor. A periodontitis, if diagnosed and treated on time, may not involve so much morbidity. Studies of periodontal disease are increasing in number and tend to show numerous links with other diseases, such as respiratory diseases, renal diseases and pregnancy accidents. This area deserves further investigation in order to understand better the details of the mechanisms that lead to such consequences.

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