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REVIEW ARTICLE

A comprehensive review: role of smokeless tobacco consumption as a risk factor for diabetes mellitus

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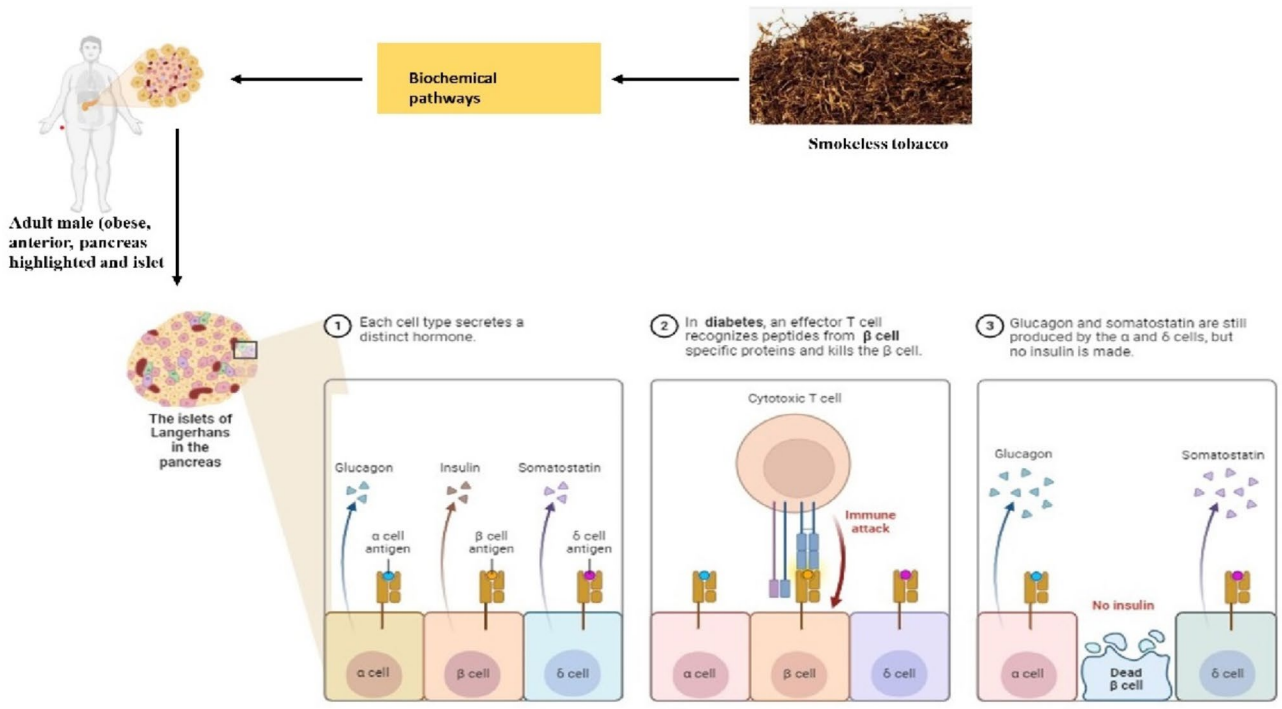
Abstract

The extensive use of smokeless tobacco and the worldwide occurrence of diabetes mellitus (DM) poses significant public health obstacles. A comprehensive review of the literature was undertaken to assess epidemiological research, clinical trials, and meta-analyses that examine the link between smokeless tobacco use and DM. The key results indicate that the biological constituents of smokeless tobacco may interfere with the process of glucose metabolism and lead to an increase in insulin resistance. An association between consumption levels and diabetes risk is evident, with higher levels of usage being positively correlated with an increased chance of developing diabetes. Smokeless tobacco usage is identified as a significant risk factor for DM. This highlights the need to implement focused public health initiatives and policies aimed at decreasing the usage of smokeless tobacco and its influence on the incidence of diabetes. Future research should prioritize elucidating the processes behind this correlation and developing efficacious preventative methods to mitigate the worldwide burden of diabetes.

Graphical abstract



Keywords Smokeless tobacco · Diabetes Mellitus · Snus · Snuff · Awareness campaigns · Smoking

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Introduction

Smokeless tobacco encompasses tobacco products that are ingested without the act of smoking. These devices are specifically engineered to dispense nicotine and other substances upon oral placement or chewing. Common varieties include chewing tobacco, which consists of ragged or warped tobacco leaves positioned between the cheek and gum; snuff, which may be either dry and inhaled via the nose or wet and inserted between the lip and gum; and snus, a moist variety of snuff that is placed beneath the upper lip [1, 2]. These items are widely embraced in many cultures, however, they pose substantial health hazards, including mouth cancer and nicotine addiction [3]. It is available in several forms, including as Extinguish: Tobacco that has been finely pulverized and may have either a dry or wet texture. Dry snuff is often inhaled via the nostrils, but wet snuff, sometimes known as dip tobacco [4], is put between the gums and cheek. Chewing tobacco refers to tobacco leaves that are larger and may be chewed or inserted between the gums and cheek. Snus is a kind of wet snuff that has its origins in Sweden. Dissolvable tobacco refers to finely powdered tobacco that is compressed into various forms such as sticks, pellets, or strips (Table 1) [5] and is designed to dissolve when placed in the mouth. Smokeless tobacco products administer nicotine and other detrimental chemicals directly into the user's body via absorption in the mouth and nose, as opposed to inhalation of smoke. Smokeless tobacco custom remains to be a substantial worldwide public health issue [6, 7].

From an epidemiological perspective, the prevalence of this condition differs significantly across different locations and demographic groups (Fig. 1).

More than 40 different types of smokeless tobacco, including pan, paan masala, khaini, zarda, mawa, gutka, mishri, and gudakhu, are consumed by chewing, snuffing, and application to the teeth and gums [23, 24]. In India, khaini is the predominant form of Smokeless Tobacco, consisting of a blend of tobacco and lime. It is used by more than 10% of smokers. Approximately 7% of the population uses gutka, a blend of tobacco, lime, and areca nut. Approximately 6% of individuals use betel quid with tobacco, while approximately 4% utilize mishri, gul, and gudakhu for oral application. Smokeless tobacco is mistakenly seen as a less risky substitute for smoking, leading to higher rates of tobacco use initiation and persistence [25]. The use of smoked and smokeless tobacco is a substantial worldwide public health hazard, leading to eight million fatalities per year and ranking as a major health issue in several countries [26, 27]. Over 66% of death rates in emerging nations are caused by non-communicable diseases, with tobacco usage being a prominent avoidable risk element. The intake of chewing tobacco, intake, and smoking are correlated with an intellectual decline in an aging population [28]. Tobacco is a highly accessible material that is readily and legally obtainable. Despite several international policy initiatives, the prevalence of tobacco usage continues to persist, and projections indicate that by 2030, an alarming 10 million premature deaths will occur annually as a direct result of tobacco use. Developing nations account for around 70% of both tobacco usage and mortality [29]. Recent studies have

Table 1 Constituents and additives of various forms of Smokeless Tobacco

Form of Smokeless Tobacco	Constituents	Additives	Forms	Common Brands	References
Snuff	Tobacco-nicotine, sugar, salt, slaked lime, spices, flavorings	Slaked lime, spices, flavorings	Powder, loose	Copenhagen, Skoal	[8, 9]
Chewing Tobacco	Larger-grain tobacco leaves, sugar, salt, spices, flavorings	Sugar, salt, spices, flavorings	Loose leaf, plug, twist	Red Man, Levi Garrett	[10, 11]
Dissolvable Tobacco	Finely ground tobacco, sweet flavors, sometimes looks like candy	Sweet flavors, binders, coloring agents	Lozenges, strips, sticks	Camel Orbs, Marlboro Sticks	[12]
Snus	Cut tobacco, sugar, salt, spices, flavorings	Salt, moisture agents, flavorings	Pouches	General, Camel Snus	[13]
Dry Snuff	Finely cut or powdered dry tobacco	Spices, flavorings	Powder	WE Garrett, Tube Rose	[14]
Moist Snuff	Cut tobacco, sugar, salt, spices, flavorings	Moisture agents, preservatives, flavorings	Loose, pouches	Copenhagen, Skoal	[15]
Dip	Moist snuff, sugar, salt, spices, flavorings	Moisture agents, preservatives, flavorings	Loose, pouches	Grizzly, Kodiak	[16, 17]
Plug	Cured tobacco in a small brick shape	Sweeteners, binders	Brick	Cannon Ball, Days Work	[18]
Twist	Cured tobacco in a rope form	Sweeteners, preservatives	Rope	Mammoth Cave, Cotton Boll	[19, 20]
Sachets	Tea bag-like pouches of dry snuff	Binders, flavorings	Pouches	General, Camel Snus	[12]
Sticks, Pellets, Strips	Finely ground tobacco, sweet flavors	Sweeteners, binders, coloring agents	Sticks, pellets, strips	Camel Orbs, Marlboro Sticks	[21, 22]

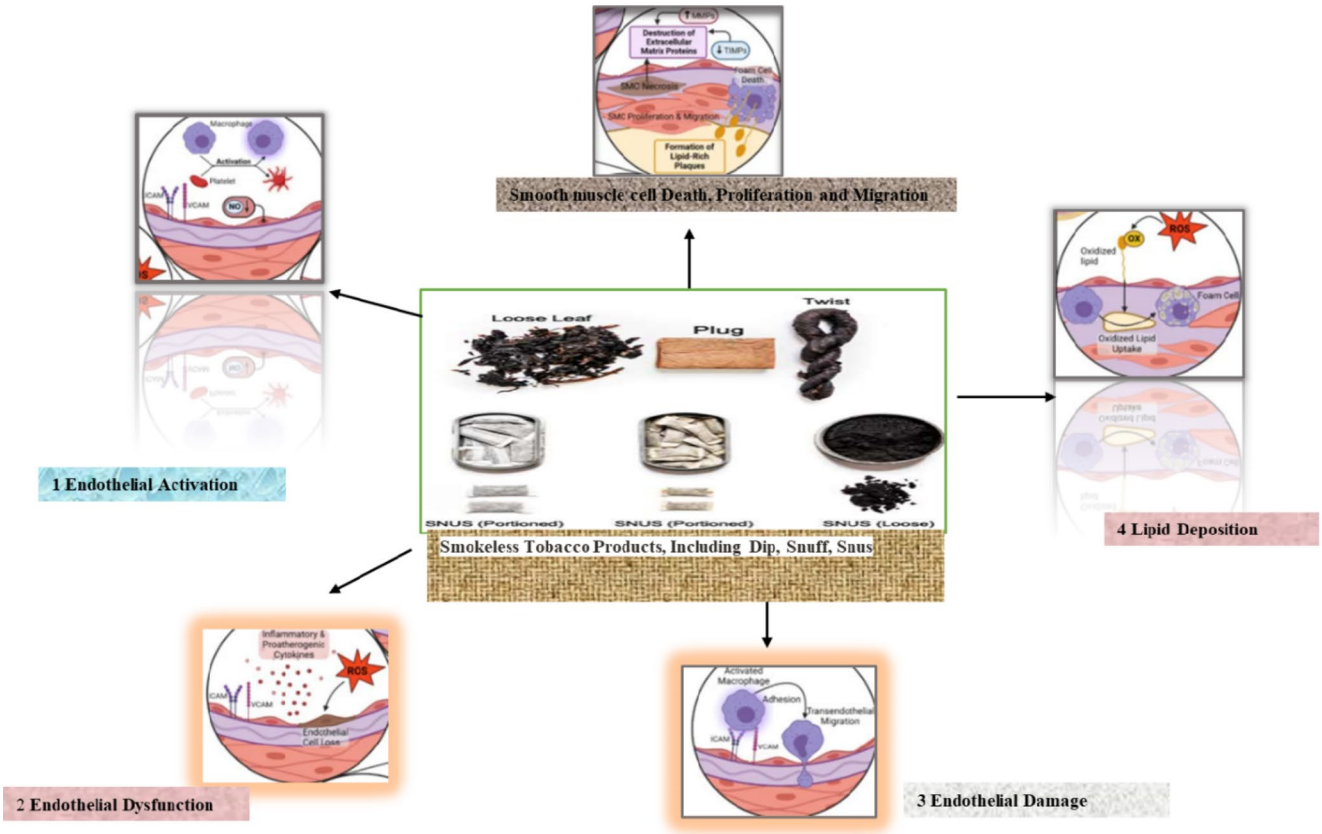

Fig. 1 The diagram illustrates the signaling pathways in the vessel wall that are triggered by smokeless tobacco. Firstly, the oxidative stress caused by smokeless tobacco activates the endothelium by increasing the expression of adhesion molecules such as intracellular adhesion molecules and vascular cell adhesion molecules. Additionally, this oxidative stress also affects macrophages and platelets

highlighted the potential role of SLT as a risk factor for the development of DM, a chronic metabolic disorder characterized by impaired glucose regulation, insulin resistance, and long-term complications affecting multiple organ systems [30].

DM, particularly type 2 diabetes, has emerged as a global health concern due to its increasing prevalence and association with lifestyle factors, including diet, physical inactivity, and substance use [31, 32]. Although cigarette smoking has been extensively studied in the context of diabetes risk, the impact of SLT on glycemic control and metabolic health remains inadequately explored [33, 34]. The toxic constituents of SLT, including nicotine, nitrosamines, and other harmful chemicals, may contribute to insulin resistance, pancreatic β-cell dysfunction, and chronic inflammation, all of which are key mechanisms in the pathogenesis of diabetes [35, 36].

This review aims to provide a comprehensive overview of the existing evidence linking smokeless tobacco consumption to DM. By examining epidemiological studies, mechanistic insights, and public health implications, this article seeks to highlight the need for further research and public health interventions to address the growing burden of diabetes-related to SLT use. Understanding this association is crucial for shaping policies and clinical guidelines aimed at reducing diabetes incidence, especially in populations where SLT use is prevalent.

Substances in smokeless tobacco that are linked to increased metabolic risks

Nicotine is a key driver of metabolic risk across all smokeless tobacco types (snus, chewing tobacco, snuff), primarily causing insulin resistance and β-cell dysfunction, with variations in risk observed between Scandinavian and U.S. studies. Nitrosamines, especially prevalent in snus and chewing tobacco, promote chronic inflammation and oxidative stress, contributing to T2D and hypertension, with geographic differences seen across populations, particularly in South Asia. Polycyclic aromatic hydrocarbons (PAHs) and heavy metals (cadmium, lead), more common in South Asian smokeless tobacco products, lead to insulin resistance and β-cell toxicity. Additionally, additives like sugar and flavoring agents, found primarily in U.S. products, contribute

to obesity and central fat accumulation, further elevating diabetes risk (Table 2).

- **Nicotine** consistently appears across all smokeless tobacco products as a key driver of metabolic risk, primarily through insulin resistance.
- **Nitrosamines** and **PAHs** show variation based on geographic differences in the formulation and preparation of tobacco products, with higher risks observed in certain populations, particularly in South Asia.
- **Heavy Metals** such as **cadmium** and **lead** tend to be more problematic in South Asian smokeless tobacco, contributing to diabetes risk via β-cell toxicity.
- **Additives** such as sugar and flavoring agents, especially in US products, may contribute to obesity and central fat accumulation, further elevating diabetes risk.

Comparative risks of cigarette smoking and smokeless tobacco use on type 2 diabetes (T2Ds) and metabolic disorders

The risks associated with cigarette smoking and smokeless tobacco use concerning T2D and metabolic disorders exhibit significant differences. Cigarette smoking is linked to a 30–40% increased risk of developing T2D compared to non-smokers, primarily due to its substantial impact on insulin resistance and central adiposity [45]. Additionally, smokers are 1.5 to 2 times more likely to develop hypertension and face strong associations with various cancers [46]. The systemic inflammation and oxidative stress promoted by cigarette smoking further exacerbate metabolic dysfunctions. In contrast, smokeless tobacco users experience a 25–30% increased risk of T2D, particularly among heavy users [47]. This risk is attributed to nicotine's role in increasing insulin resistance and the β-cell toxicity resulting from heavy metals found in smokeless tobacco. While smokeless tobacco poses a lower risk than cigarette smoking, it still significantly contributes to conditions such as hypertension and chronic inflammation, with heightened risks particularly noted in South Asian populations [48]. Overall, while both forms of tobacco have detrimental metabolic impacts, the severity and nature of these risks vary considerably.

Association between Smokeless tobacco use and DM

Studies like the Stockholm Diabetes Prevention Programme have indicated that snus users have a higher risk of developing T2D, likely due to nicotine-induced insulin resistance and β-cell dysfunction, although smoking history was not fully controlled in these studies [49, 50]. However, the Swedish MONICA study found no significant link between snus use and diabetes when smokers were excluded, suggesting nicotine's impact may be minimized when smoking is accounted for, though the small number of heavy users led to inconsistent risk estimations. Nicotine contributes to

Table 2 Summarizing the specific substances in smokeless tobacco that are linked to increased metabolic risks, highlighting whether these risks differ across various types of smokeless tobacco and populations based on the studies:

Substance	Type of Smokeless Tobacco	Metabolic Risk	Mechanisms	Population/Study Variations	References
Nicotine	Snus, Chewing Tobacco, Snuff	Increased insulin resistance, β-cell dysfunction	Impairs glucose metabolism and causes central adiposity	Higher in snus users; inconsistent across Scandinavian and US studies	[37]
Nitrosamines	Snus, Chewing Tobacco, Betel Quid	Increased risk of T2D, hypertension	Promotes chronic inflammation, oxidative stress	Present in higher concentrations in snus; lower in some Asian populations	[38]
Polycyclic Aromatic Hydrocarbons (PAHs)	Chewing Tobacco, Snuff	Insulin resistance, dyslipidemia	Causes endothelial dysfunction, inflammation	Found more commonly in smokeless tobacco from South Asia	[39]
Heavy Metals (Cadmium, Lead)	Chewing Tobacco, Snuff	Impaired glucose tolerance, hypertension	Toxicity to pancreatic β-cells	Levels vary geographically; more common in South Asian products	[40]
Acetaldehyde	Snus, Chewing Tobacco	Increased risk of insulin resistance and metabolic syndrome	Disrupts cellular metabolism and promotes fat accumulation	Found in higher concentrations in fermented tobacco products	[41]
Carcinogenic Volatile Nitrosamines (CVNAs)	Snus, Chewing Tobacco	Higher risk of diabetes-related complications	Promotes DNA damage, disrupts glucose regulation	Highest in US smokeless tobacco products; lower in Swedish snus	[42]
Ammonia	Snuff, Chewing Tobacco	Risk of insulin resistance	Alters systemic pH, contributing to β-cell stress	Common in African and South Asian tobacco products	[43]
Other Additives (Sugar, Flavoring Agents)	Snus, Chewing Tobacco	Obesity, central adiposity, increased diabetes risk	Encourages excess calorie intake, metabolic disturbances	Common in flavored snus and chewing tobacco used in the US	[44]

Key Points:

insulin resistance by impairing the body's response to insulin and promoting β-cell dysfunction, leading to increased blood glucose levels over time [51–53]. Chronic systemic inflammation caused by nicotine also damages pancreatic β-cells, further contributing to diabetes development [54]. Nicotine's endothelial dysfunction disrupts glucose regulation, promoting metabolic dysfunction [55, 56].

Smokeless tobacco, such as snuff and snus, increases insulin resistance and inflammation due to high nicotine levels, raising diabetes risk by 25-30% in heavy users [57, 58]. Cigarette smoking exacerbates central adiposity and damages β-cells, increasing diabetes risk by around 40% [59]. Various factors affect this risk, such as body mass index (BMI), where a higher BMI leads to increased insulin resistance and central fat accumulation, even though smokeless tobacco use is linked to lower BMI but central fat accumulation [60, 61]. Gender and ethnicity also play a role, with men using smokeless tobacco more frequently, leading to different patterns of insulin resistance, while African Americans have a higher prevalence of menthol cigarette use compared to lower smoking rates among Hispanics [62–64].

Changes in tobacco products, such as the introduction of filters and reduced tar cigarettes, have altered harmful constituent exposure but have not significantly lowered diabetes risk [65, 66]. Additionally, the curing processes and flavorings in snuff and snus have increased nicotine levels, which may further contribute to insulin resistance, though the full health impact of these changes remains under study [67] (Fig. 2) (Table 3).

Identification of diabetes cases

We used all accessible data gathered in each research to ascertain the presence of diabetes at the beginning and the occurrence of diabetes over the subsequent period of observation. T2D diagnoses were discovered by examining several sources and dated based on the earliest available record [68, 69]. The research gathered documented diagnoses from hospital admissions from 1987 and outpatient specialist treatment since 2001 by linking records to the National Patient Register. This was done using the unique personal identity number issued to all Swedish citizens [70, 71]. This registry includes data on primary and secondary diagnoses that are classified using the Swedish version of the International Classification of Disease ninth revision from 1986 to 1996, with code 250 representing diabetes. From 1996 onwards, the registry used the ICD-10 classification system, with code E11 for T2D and code E14 for unspecified diabetes. Furthermore, the Prescribed Drug Register 31 was used to get prescriptions for glucose-lowering medications in all of the investigations. The national register maintains a comprehensive record of all prescriptions made since July

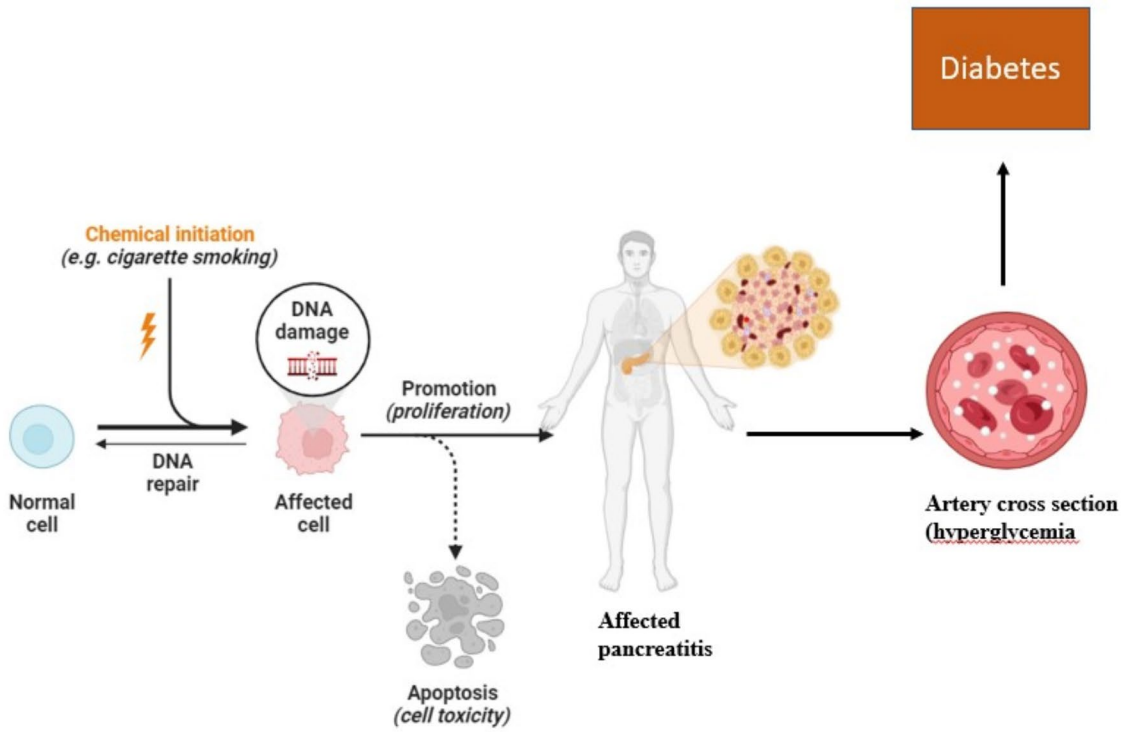

Fig. 2 The relationship between smoking, affected pancreatitis and diabetes

Table 3 Association between smokeless tobacco use, diabetes risk, and key mechanisms

Aspect	Details/Findings	Mechanisms Identified	Confounding Factors/ Variables	Source(s)
Study Type	**Stockholm Diabetes Prevention Programme**: Snus users have higher risk of developing T2D.	Nicotine causing insulin resistance, β-cell dysfunction.	Smoking history not fully controlled.	[49]
	Swedish MONICA Study: No significant link between snus and diabetes when excluding smokers.	Nicotine-induced insulin resistance minimized by excluding smokers.	Small number of heavy users led to inconsistent risk estimations.	[50]
Nicotine Impact on Health	**Insulin Resistance**: Nicotine impairs the body's response to insulin.	Increased blood glucose levels over time.	Influence of tobacco components not isolated in all studies.	[51, 52
	Systemic Inflammation: Chronic inflammation damages pancreatic β-cells.	Leads to impaired insulin secretion and diabetes development.	N/A	[54]
	Endothelial Dysfunction: Nicotine causes blood vessel damage.	Disrupts glucose regulation, promoting metabolic dysfunction.	N/A	[55, 56]
Tobacco Type	**Smokeless Tobacco**: Increases insulin resistance and inflammation.	High nicotine levels impair glucose metabolism, causing diabetes.	25-30% increased diabetes risk in heavy users.	[57, 58]
	Cigarette Smoking: Increases central adiposity and β-cell damage.	Promotes fat accumulation in the central body, worsening insulin sensitivity.	40% increased diabetes risk in smokers.	[59]
Variables Affecting Risk	**Body Mass Index (BMI)**: Higher BMI leads to increased insulin resistance and central adiposity.	Smokeless tobacco is linked to lower BMI but central fat accumulation.	The influence of BMI varies with smoking habits.	[60, 61]
	Gender: Differences in tobacco use may alter risk.	Men use smokeless tobacco more frequently; with differing patterns of insulin resistance.	Varies across genders, impacting insulin sensitivity.	[62]
	Ethnicity/Race: Cultural habits influence tobacco use and risk.	African Americans are more likely to use menthol cigarettes, while Hispanics have lower smoking rates.	Patterns of use impact diabetes risk across ethnicities.	[63, 64]
Changes in Tobacco Products	**Cigarettes**: Filters (1950s) and reduced tar cigarettes (1980s) changed exposure levels.	Reduced harmful constituent exposure but did not lower diabetes risk.	Variations in constituents affect risk.	[65, 66]
	Snuff/Snus: Flavorings and curing processes altered nicotine levels.	Higher nicotine levels may increase insulin resistance.	The influence of changes in nicotine content on health remains under study.	[67]

2005, organized according to the Anatomical Therapeutic Chemical categorization system. The Anatomical Therapeutic Chemical group A10, which includes insulin and oral antidiabetic medications, was used for the identification of diabetes. Furthermore, all the studies included data on self-reported diabetes at the beginning of the study, as well as at different points throughout the follow-up period in three specific studies (Västerbotten Intervention Programme, Stockholm Public Health Cohort, and Malmö Diet and Cancer Study). Additionally, individuals from two separate studies, namely the Västerbotten Intervention Programme and Malmö Diet and Cancer Study, were subjected to oral glucose tolerance tests at the beginning and throughout the study. Those with 2-hour glucose levels equal to or greater than 12.2 mmol L^{-1} (measured from capillary blood) were categorized as having diabetes according to the guidelines set by the World Health Organisation. The Malmö Diet and Cancer Study collected data from a local diabetes registry and the National Diabetes Register to identify 32 cases. To differentiate between T2D and type 1 diabetes, we omitted all instances that occurred before the age of 35 and those that had a documented diagnosis of type 1 diabetes according to the patient registries.

Factors influencing the relationship

Several crucial variables determine the connotation between the custom of smokeless tobacco and DM. The components included in smokeless tobacco products may result in insulin resistance, a disease that hampers the body's capacity to adequately manage blood sugar levels. The presence of compounds such as nicotine and other toxic components in tobacco worsens this resistance by disrupting glucose metabolism. Smokeless tobacco use is often linked to bad lifestyle practices, including inadequate dietary choices and a sedentary lifestyle. These behaviors are substantial contributors to the development of diabetes [69, 72]. These behaviors may main to a rise in body weight and disruption of metabolic function, which in turn raises the chances of

developing insulin resistance and T2D. Genetic predisposition influences how people react to the harmful substances found in smokeless tobacco. Individuals with certain genetic predispositions may exhibit increased susceptibility to developing diabetes since their genetic composition might combine with environmental influences such as tobacco smoking. Comprehending these intricate interconnections is crucial for healthcare personnel to formulate efficient tactics for avoiding and controlling diabetes in persons who use smokeless tobacco. The statement emphasizes the need to implement a thorough health education program, conduct individualized risk evaluations, and provide assistance for quitting tobacco to reduce these dangers and enhance overall health results [73, 74]. The usage of smokeless tobacco is strongly correlated with an elevated risk of developing T2D Mellitus. In case-control research, it was shown that 19.1% of individuals with diabetes were users of smokeless tobacco in comparison to 14.2% of those without diabetes. Additionally, the research revealed that obesity, a family past of diabetes, and corporal dormancy were all notable risk factors for T2D Mellitus [36, 60]. The correlation between tobacco use and insulin resistance or the development of diabetes is sometimes ambiguous. Multiethnic cohort research could not find any separate connection between tobacco smoking and insulin resistance or the likelihood of developing T2D Mellitus. The authors propose that the link may be more intricate than previously believed and requires more examination. Potential determinants of the association between tobacco and diabetes include race/ethnicity, gender, body mass index, and patterns of tobacco use. Smoking behaviors vary across different racial/ethnic groups, which may result in different levels of exposure and impact on insulin resistance and the risk of developing diabetes [75–77]. Despite the common belief that smokeless tobacco smokeless tobacco may be a safer alternative to smoking cigarettes, it contains equal or higher amounts of nicotine and is as, if not more, addictive, depending on its composition. Based on the research, it seems that using smokeless tobacco might have additional negative consequences in individuals with diabetes, leading to higher rates of illness and earlier death [78]. This study aims to assess the occurrence of problems related to diabetes in a group of diabetic patients, to determine whether the use of snuff tobacco is a contributing factor to overall mortality, diabetic nephropathy, and diabetic retinopathy.

Public health implications

The policy implications for tobacco control and diabetes prevention require harmonizing policies to minimize common risk factors and enhance overall public health. Policymakers can improve awareness, enforce legislation, and allocate resources more efficiently by combining their efforts. This involves cultivating collaborations, executing focused interventions, and giving priority to education to decrease the occurrence of both tobacco use and diabetes, therefore enhancing the overall well-being of the community [79]. Smoking is a substantial menace factor for developing T2D, increasing the risk by 30–40% compared to non-smokers. Smokers with diabetes are more likely to experience grave health problems, with heart disease, kidney disease, vision loss, and limb amputations [35, 80, 81] The Epidemiological Study of Risk Factors for LADA and T2D (ESTRID) is a research project conducted in Sweden. It is a population-based case-control study that is part of the All New Diabetics in Scania registry and biobank. The main objective of ESTRID is to analyze and describe the clinical and genetic characteristics of all newly diagnosed diabetes cases in Scania County. ESTRID has been registering new instances of LADA and T2D from All New Diabetics in Scania since 2010 [82]. Questionnaires are used to gather lifestyle and demographic information, which are given to patients shortly after diagnosis (with a median time of 4.9 months). Matched controls are picked at random from the whole population of Scania using incidence-density sampling [83, 84]. These controls are responsive to the questionnaire, but they do not provide blood samples for genetic studies. Thus, this investigation included a group of individuals without diabetes, selected from the general community, who served as controls in the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study. The EIRA study is a case-control study that has a similar design to the ESTRID study. The prevalence of rheumatoid arthritis is higher in women compared to males, as shown by a greater representation of women in the control group of this research. Therefore, the 'genetic' controls are carefully selected to be of the same sex and age as the patients. Governments must give priority to implementing comprehensive tobacco control measures as a very effective approach to prevent and manage diabetes. It is essential to create strong surveillance systems to monitor tobacco use, exposure, and the effects of tobacco control efforts. This involves incorporating tobacco monitoring into national health surveys and using instruments such as the Global Tobacco Monitoring System (GTSS) [85, 86]. Imposing higher taxes on tobacco products is a very successful strategy for decreasing tobacco use, particularly among young people and those with low incomes. Governments should enforce and periodically raise tobacco taxes [87, 88]. It is crucial to implement and enforce inclusive smoke-free regulations that ban smoking in all indoor public and workrooms to safeguard individuals from secondhand smoke and to discourage the act of smoking. Implementing comprehensive prohibitions on

tobacco publicizing, elevation, and sponsorship may have a substantial impact on reducing tobacco usage and thwarting the tobacco industry's tries to challenge public health initiatives [80, 89]. Offering cost-effective and easily obtainable cessation options, which include behavioral assistance and medication, may substantially enhance the likelihood of successful smoking cessation endeavors among those who smoke, including those diagnosed with diabetes. Executing meticulously planned public education programs may enhance knowledge about the correlation between smoking and diabetes, as well as the advantages of cessation, to inspire and facilitate behavioral modification. Governments may successfully improve public health outcomes and reduce the burden of associated epidemics, such as diabetes, by enacting a comprehensive set of evidence-based tobacco control strategies [90–92]. Intervention and cessation programs should prioritize a complete strategy that incorporates education, accessibility, and community support. This involves initiating focused public awareness initiatives to emphasize the health hazards linked to tobacco use and its correlation with diabetes [93]. It is essential to guarantee the convenient availability of evidence-based stop treatments, including counseling and nicotine replacement medications. Moreover, the incorporation of cessation assistance within healthcare settings, such as primary care and diabetes management programs, improves efficacy. Enhancing regulatory measures, such as implementing more stringent rules on tobacco sales and creating smoke-free areas, further bolsters these efforts. Finally, cultivating collaborations with nearby communities and organizations may provide crucial support systems for those endeavoring to quit smoking and properly control their diabetes [94].

Health education and awareness campaigns

Public health necessitates the implementation of health education and awareness initiatives that focus on the correlation between the practice of smokeless tobacco and DM. The purpose of these initiatives is to increase awareness of the substantial hazards linked to smokeless tobacco, which is commonly considered a less harmful substitute for smoking. Smokeless tobacco, on the other hand, may result in significant health problems, such as an elevated likelihood of developing DM. Through the spreading of evidence on the detrimental consequences of smokeless tobacco, including its influence on blood glucose levels and insulin resistance, these initiatives may promote the adoption of healthier alternatives [95]. Emphasizing the correlation between the practice of smokeless tobacco and the development of diabetes-related consequences, such as cardiovascular ailments and nerve impairment, might serve as an additional incentive for persons to refrain from or cease using these products [96]. Efficient campaigns may use many channels, such as social media and community outreach, as well as collaborations with healthcare practitioners, to provide information and offer assistance for cessation endeavors. This strategy not only aids in decreasing the incidence of smokeless tobacco use but also improves diabetes control and overall health outcomes (Fig. 3).

Clinical considerations

Smokeless tobacco usage, including items such as eating tobacco and snuff, is often realized as a comparatively less hazardous substitute for smoking. Nevertheless, recent data suggests that smokeless tobacco might provide substantial health hazards, such as an increased likelihood of acquiring DM [72]. The prevalence of smokeless tobacco (ST) usage among patients with T2D mellitus in South Asia is 24.08%. Age, gender, obesity, family history of diabetes, and physical inactivity are important issues that are strongly linked to the development of T2D mellitus among smokeless tobacco users [60]. Gutkha is the main ST product used by diabetics. Smokeless tobacco (ST) consumption is associated with a higher risk of developing T2D mellitus, with an odds ratio of 1.39. Nevertheless, it is crucial to acknowledge that this relationship does not achieve statistical significance. Nicotine included in smokeless tobacco (ST) products leads to insulin resistance and increased cortisol levels, which in turn leads to elevated blood glucose levels. Acrolein, a secondary product resulting from the burning of tobacco, has the potential to play a role in the progression of T2D mellitus and insulin resistance. The patient records were retrieved from the electronic clinical record system used in the diabetic clinic. For this research, all patients who were over 18 years old when they entered the clinic, diagnosed with either type 1 diabetes or T2D, and had been followed up at the clinic for at least one year or had attended a minimum of two clinic visits, were considered eligible for inclusion. Patients were eliminated from the trial if there were substantial gaps in the data about smoking or snuff usage. Patients were disqualified if their national identity number was not entered into the computerized system, including non-SA nationals who were not permanent residents. The rationale for omitting patients without an identity number is that the determination of their survival status is contingent upon the possession of a national identification number issued by the Department of Home Affairs. Since 2009, the KPTH diabetes clinic has been using an electronic record-keeping system (MS Access; Microsoft Corp, Redmond, WA, USA) to collect all clinical information of patients. Data that is pertinent to the research was taken from this record-keeping system. The study collected clinical data, tobacco-related

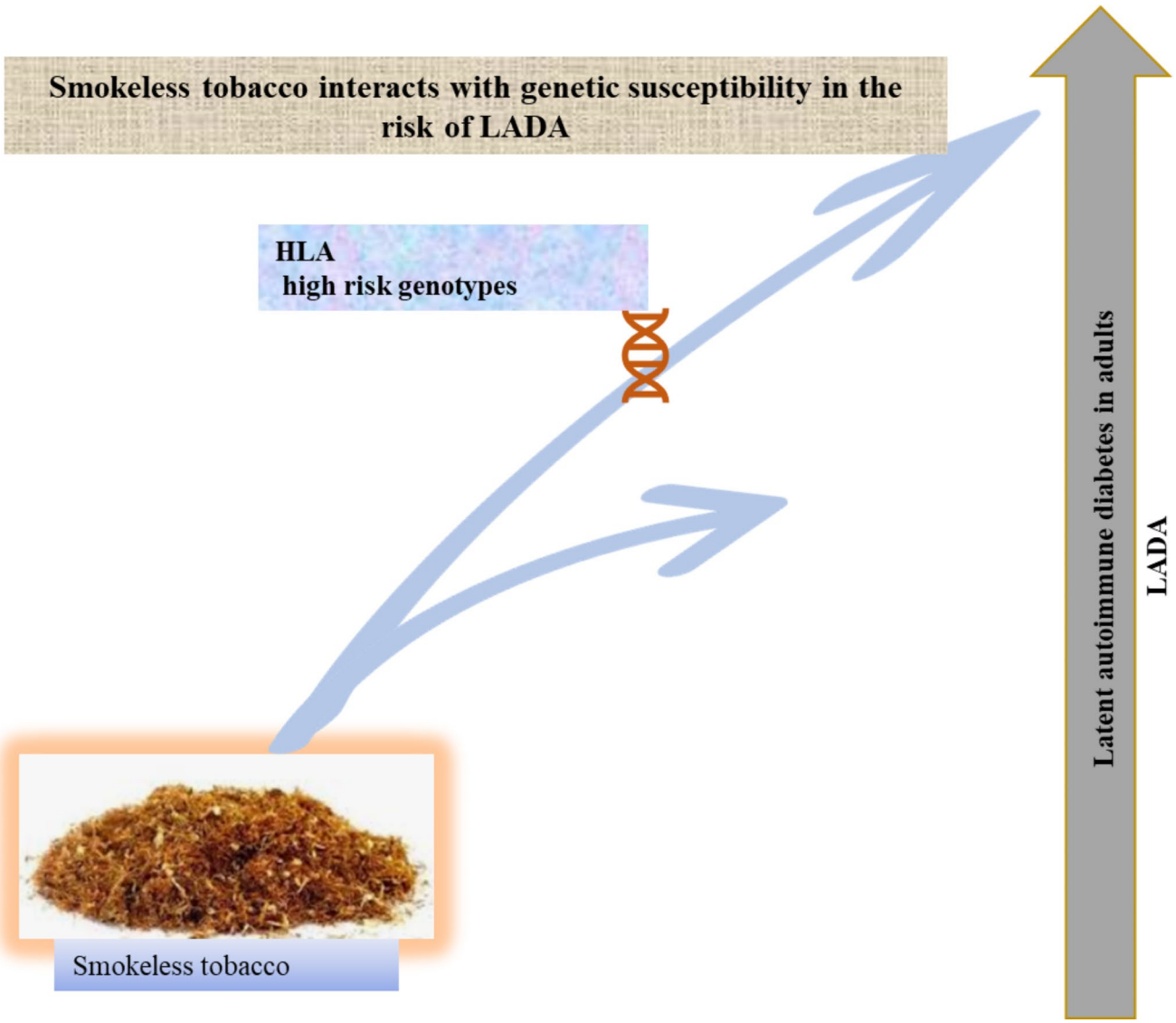

Fig. 3 Investigation of the correlation between smokeless tobacco use, HLA genotypes, and the occurrence of latent autoimmune diabetes in people

data, and outcome measurements. This included all factors that may influence the link between tobacco use and the outcome variables. The extracted patient data from the database included demographic information, clinical observations, and laboratory results [97] (Table 4).

Future directions and research needs

Future research should prioritize investigating the mechanisms that connect smokeless tobacco use to diabetes, performing extensive prospective studies to accurately measure the risk, and evaluating the effects of quitting smokeless tobacco and implementing tobacco control programs (Table 5). Implementing this comprehensive strategy will contribute to the advancement of our knowledge and guide for reducing the impact of smokeless tobacco practice and its link to T2D.

Conclusion

This comprehensive review highlights the significant role of smokeless tobacco consumption as a risk factor for developing DM, particularly T2D. Substances such as nicotine, nitrosamines, polycyclic aromatic hydrocarbons (PAHs), heavy metals, and various additives contribute to insulin resistance, β-cell dysfunction, and systemic inflammation, all of which are critical pathways leading to metabolic disorders. Nicotine, the most prominent agent, consistently impairs glucose metabolism and promotes central adiposity, while nitrosamines and heavy metals further exacerbate

Table 4 Clinical consideration and prevalence and risk factors of smokeless tobacco use in diabetes

Topic	Specific Focus	References
Prevalence and Risk Factors of Smokeless Tobacco Use in Diabetes	The pooled prevalence of ST practice among T2D mellitus patients in South Asia is 24.08%	[30, 72]
	Factors associated with T2D mellitus in ST users include age, gender, obesity, family history of diabetes, and physical inactivity.	[60]
	The most commonly used ST product among diabetics is gutkha	[98]
Association Between Smokeless Tobacco and T2D	ST routine is a danger factor for developing T2D mellitus, with an odds ratio of 1.39	[30]
	Nicotine in ST products contributes to insulin resistance and increased cortisol levels, leading to elevated blood glucose levels.	[99]
	Acrolein, a combustion product of tobacco, may also show a role in T2D mellitus and insulin resistance.	[30]
Limitations and Future Research Directions	A limited number of studies investigating the ST- T2D mellitus association in the Southeast Asia Region (SEAR)	[100]
	Myanmar, Bhutan, Timor Leste, and Sri Lanka are not represented.	[60]
	This indicates by the pooled Hazard Ratio that high consumption of smokeless tobacco increases the risk factor of T2D mellites.	[60]

Table 5 Future directions and Research needs in smokeless tobacco use and DM

Research Area	Specific Focus	Potential Impact	Examples of Studies	References
Mechanistic Studies	Investigate biochemical pathways linking smokeless tobacco to diabetes onset.	Better understanding of disease mechanisms.	Identify biomarkers of risk and progression.	[60, 101, 102]
	Explore genetic susceptibility factors.	Personalized medicine approaches.	Genome-wide association studies (GWAS).	[73, 103]
Longitudinal Studies	Conduct long-term studies to assess the chronic impact of smokeless tobacco.	Establish causality and timeframes.	Prospective cohort studies tracking health outcomes.	[104–108]
	Track progression from smokeless tobacco use to diabetes development.	Inform preventive strategies.	Detailed patient follow-ups and health monitoring.	[106, 109–112]
Population Studies	Analyze data across diverse populations to identify high-risk groups.	Tailored interventions for different demographics.	Cross-sectional studies comparing different population segments.	[109, 113–115]
	Examine the role of socioeconomic factors.	Address health disparities.	Studies on income, education, and access to healthcare.	[10, 52, 116–118]
Intervention Strategies	Develop and test targeted cessation programs.	Reduce the incidence of smokeless tobacco use and related diabetes.	Randomized controlled trials of cessation methods.	[116, 119–123]
	Evaluate the effectiveness of public health campaigns.	Improve public health outcomes.	Surveys and outcome assessments post-intervention.	[124–129]
Policy Research	Assess the impact of regulatory measures on smokeless tobacco use.	Inform policy and regulation.	Studies on the effect of bans, restrictions, and taxation.	[130–134]
	Advocate for stricter resistor and taxation policies.	Potentially reduce the use and prevalence of diabetes.	Policy analysis and comparison across regions/countries.	[135–139]
Health Education	Enhance awareness programs highlighting the risks of smokeless tobacco.	Increased public knowledge and preventive behavior.	Development and dissemination of educational materials.	[59, 140–144]

metabolic disturbances by inducing chronic inflammation and β-cell toxicity. Importantly, the risks associated with smokeless tobacco products vary geographically and across populations due to differences in the formulation and preparation methods, with higher risk levels often observed in South Asian and African populations due to the presence of more harmful substances, such as heavy metals and higher levels of nitrosamines.

While certain products like Swedish snus present comparatively lower risks, the growing global prevalence of smokeless tobacco usage, combined with its unique metabolic hazards, calls for more targeted public health strategies and greater awareness of its potential to aggravate diabetes risk. Further research is needed to better understand the long-term impacts of smokeless tobacco on glucose metabolism and to develop effective interventions for reducing its use as a modifiable diabetes risk factor.

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