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Review

Diabetes in the practice of otolaryngology

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ABSTRACT

Diabetes mellitus is the most common endocrine disease, characterized by chronic hyperglycemia. The hyperglycemic milieu leads to endothelial injury in blood vessels of variant size, which results in microangiopathy and macroangiopathy (atherosclerosis). Consequential ischemia of nerves and hyperglycemia by itself lead to nerve degeneration and generalized neuropathy, affecting most often the sensory peripheral nerves and the autonomic nervous system. Auditory, vestibular and olfactory sensorium may be compromised by DM.

People with DM have an increased susceptibility to infection, as a result of neutrophil dysfunction and impaired humoral immunity. Therefore DM predisposes to certain infectious diseases, such as fungal sinusitis or malignant otitis externa, which are rare in general population. Recovery from infections or from injuries may be compromised by coexisting DM.

In this review we discuss complications of DM in the head and neck region. Otolaryngologists and general practitioners should be alert to specific conditions related to DM and be minded of the relevant complications and consequences.

1. Introduction

Diabetes mellitus is the most common endocrine disease, characterized by chronic hyperglycemia. Type 2 (DM) is the most prevalent type of diabetes, affecting millions of people over the world, with increasing incidence and prevalence [1–3].

The hyperglycemic milieu leads to endothelial injury in blood vessels of variant size, which results in microangiopathy and macroangiopathy (atherosclerosis) [3]. Consequential ischemia of nerves and hyperglycemia by itself lead to nerve degeneration and generalized neuropathy, affecting most often the sensory peripheral nerves and the autonomic nervous system [4,5]. Auditory, vestibular and olfactory sensorium may be compromised by DM [6–8].

People with DM have an increased susceptibility to infection, as a result of neutrophil dysfunction and impaired humoral immunity [9,10]. Therefore DM predisposes to certain infectious diseases, such as fungal sinusitis or malignant otitis externa, which are rare in general population [11,12]. Recovery from infections or from injuries may be compromised by coexisting DM [13–16].

In this review we discuss complications of DM in the head and neck region. The otolaryngologist should be alert to specific conditions related to DM and be minded of the relevant complications and consequences.

2. Otitis externa

Patients with DM are susceptible to infections of the external auditory canal. They are inclined to both bacterial and fungal infections [17]. Diabetic macroangiopathy and microangiopathy compromise tissue perfusion which contributes to the pre-existing immune dysfunction and incomplete healing [18]. Microangiopathy is often aggravated by infection with *pseudomonas aeruginosa*, the most common pathogen in these infections [19,20]. Furthermore, the cerumen of the diabetic patient has higher pH, which makes environment more hospitable for pathogens [21].

Acute otitis externa, a common bacterial infection, is characterized by rapid onset otlagia with diffuse inflammation of the external ear canal. It can be preceded by aural irrigation that should be avoided in diabetics. Whenever this diagnosis is suspected in patients with DM, systemic antibiotic in addition to topical therapy should be prescribed [22]. When the infection spreads further into

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structures surrounding the external auditory canal, malignant (necrotising) otitis externa (MOE) may follow.

MOE is a rare and potentially life threatening infection of the external auditory canal, mastoid and skull base [23–26]. Most commonly MOE occurs in patients with DM (75–90%), especially in the elderly [23,27]. Hyperglycemia, however, does not appear to correlate with the risk of disease [28]. Most patients describe severe otalgia, most notably nocturnal [28]. Less commonly, impaired pain perception secondary to diabetic neuropathy and microangiopathy may obscure disease presentation and delay diagnosis [29]. Cranial nerve function may be affected as the infection progresses, the facial nerve is most commonly involved. Involvement of the glossopharyngeal, vagus, accessory and hypoglossal nerves is less common [24,30,31]. DM is associated with increased risk of cranial nerve involvement. Surprisingly, sepsis was described less often in MOE patients with DM than without. However, it is controversial whether the prognosis is affected by DM [32–34].

Treatment of MOE includes topical and systemic antibiotics, administered as an outpatient treatment or during hospitalization [23,35,36]. Hospital admission is typically reserved for patients requiring parenteral antibiotics with or without central catheter line placement [32,37]. It has been reported that patients with MEO and DM required longer and more costly hospital stay, and had higher rates of central catheter placemats than non-diabetic counterparts [32]. Tight glycemic control is considered essential for recovery by several authors, though it was difficult to achieve during the acute infection [38]. Surgical debridement and hyperbaric oxygen therapy are also accepted treatment modalities, with questionable efficacy [39–41].

3. Auditory dysfunction

Hearing impairment is a devastating disability affecting up to 2/3 of elderly population [42], associated with depression, social isolation, cognitive decline and even increased mortality [43]. A large number of population based studies have examined the association between DM and hearing loss. Most [44–50], but not all [42,51], found a significant association between the prevalence of DM and hearing loss. The reported incidence of hearing impairment among diabetics was 1.5–2.5 times fold that of an age matched control group [49,52].

Hearing loss in diabetics is primarily sensorineural, slowly progressive and bilateral [44–46]. Sudden unilateral hearing loss was also recognized, as in sudden deafness [53]. Hearing was impaired in diabetics at all frequencies, the impairment was more pronounced at high frequencies, especially 6 and 8 kHz [49]. Poor speech perception in noise among diabetics was also described, while discrimination scores were normal [54,55]. A stronger relationship between diabetes and hearing loss was found in younger patients (<70 years), suggesting presbyacusis might mask the expected diabetes-related hearing decline [56,57]. It is not clear whether glycemic control affects hearing performances [52,58,59]. Diagnosis of diabetic nephropathy with albuminuria is in correlation with hearing impairment severity [60]. Some researchers reported that DM patients are more prone to noise induced hearing loss with normal to diminished hearing recovery after noise exposure [61,62]. Furthermore, the prognosis of hearing improvement in patients with DM and sudden deafness is unfavourable [53].

Several pathophysiological mechanisms underlie hearing loss in DM. Evidence suggesting damage to the chochlea secondary to microangiopathy and local ischemia is numerous. They demonstrated thickening of the blood vessels' wall in the basal membrane and of capillaries' wall in the striae vascularis with resultant atrophy of the striae vascularis. Additionally, a significant reduction in the number of outer hair cell in the basal part of the cochlea was reported [57,63–65]. The vasa vasorum surrounding the vestibulocochlear nerve was damaged, suggestive of diabetic neuropathy [57,66].

Retro-cochlear neural pathways were also found to be impaired in diabetics [49,57,67]. Auditory brainstem response (ABR) studies report significantly delayed latencies along several parts of the nerve conduction pathway, especially in wave V [49]. An increased incidence of delay was associated with longer duration of DM [49]. Two signaling factors contribute to neuronal degradation seen in diabetics: neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF) [68,69].

Diabetes and ageing seem to share a common pathway of hearing impairment development [70]. Oxidative stress and atherosclerosis which develop with aging are augmented by DM [71,72]. Furthermore, induction of DM in mice increased the rates of age-related hearing impairment [73]. Mitochondrial damage appears to play a role in both age-related and genetic causes of diabetes induced hearing loss [74,75]. Maternally inherited diabetes and deafness (MIDD) occur secondary to mitochondrial defect and manifest with diabetes [76].

4. Vestibular dysfunction

Instability is a common manifestation of unbalanced DM, balance and gait are affected and predispose to recurrent falls [77,78]. Furthermore, diabetic patients have an increased risk for more severe injuries in fall accidents [79]. Diabetic peripheral neuropathy decreases vibration sensation, pressure sensitivity and proprioceptive feedback. These sensory feedbacks are important for maintaining balance and gait stability and may be impaired in diabetics [80–82]. Visual signals help compensate for sensory deficits, this may be further compromised by diabetic retinopathy [80,83].

The vestibular system also has an important role in maintaining position, proper movement and stable gaze [84], it is known to be adversely affected by DM. The risk of vestibular dysfunction was reported to be 70% higher in patients with DM than in age matched controls [85]. High prevalence was particularly noticed in patients older than 60 years old and in those with multiple comorbidities [86]. The prevalence of vestibular dysfunction corresponds with the duration of DM. Patients with history of DM of up to 5 years had a 41% prevalence of vestibular dysfunction, whereas a 61% prevalence was observed in patients with DM duration of 6 years and above. Poor glycemic control, as represented by HbA1c levels, was also found to increase the prevalence of vestibular dysfunction. Furthermore, vestibular dysfunction was more prevalent in patients with diabetic peripheral neuropathy (76% vs 49%) and retinopathy (71% vs 45%) [86].

Benign paroxysmal positional vertigo (BPPV) is a common vestibular condition manifested by transient position dependent vertigo and caused by dislodged otoconia [87]. The prevalence of DM was reported significantly higher in patients with BPPV than in the general population [88]. In addition, comorbidities such as DM, hypertension and osteoarthritis have been shown to increase the rate of recurrence of BPPV. The mechanism responsible for the increased risk of otoconia dislodgment in DM is unknown, theoretically it can be attributed to macular degeneration secondary to microangiopathy related local ischemia or to vestibular nerve degeneration [89].

There are evidence of vestibular dysfunction in different ENT clinical assessments. High proportion of DM patients had pathologic modified Romberg testing [85]. Caloric stimuli and rotational chair testing were found abnormal in diabetics in several studies [90]. Other studies report significant abnormalities in the phase of

VOR and the optokinetic reflex of diabetics [91]. However, another study using head thrust testing revealed lateral and superior semicircular canal dysfunction with relative sparing of the posterior canal [90]. The function of otoconial organs, the utricle and saccule, was demonstrated impaired using O-VEMP and C-VEMP [90–95].

Morphological and physiological changes in the peripheral vestibular apparatus have been reported in pathological reports and in animal models with DM. Overproduction of extracellular matrix and higher incidence of lysosomes and lipid droplets were evident in the connective tissue of the utricle and saccule [96]. Hair cell degeneration was noted, with a more prominent injury to type 1 hair cells in the saccule [96,97]. The damage to the sensory epithelium of saccule was considered to be mediated by selective insulin receptors and by specific sensitive transporters [98]. Imaging of the vestibulocochlear nerve revealed thinner nerve diameter due to smaller axonal fiber diameter and impaired myelin [99,100]. Moreover, pathologic changes characteristic of diabetic microangiopathy were observed in some but not in all analyses [101].

5. Facial nerve dysfunction

Bell's palsy is defined as acute unilateral peripheral facial palsy. It accounts for 60–75% of all cases of acute peripheral facial nerve palsy [102]. The etiology of Bell's palsy is unknown but infection with herpes virus is the most supported theory [103]. Epidemiological studies demonstrated that Bell's palsy is more frequently observed in patients with DM [104–106]. Among patients with Bell's palsy, up to 39% were diagnosed with diabetes or with prediabetes conditions (impaired glucose tolerance or impaired fasting glucose) [107]. It has been reported that facial paralysis develops more frequently in mice with DM than without DM, when inoculated with HSV-1 [108]. This enhanced reactivation could be attributed to T-cell immunity impairment secondary to DM that permits herpes virus reactivation [109,110].

Bell's palsy can develop regardless of DM severity [111]. The majority of diabetic patients with facial palsy had incomplete palsy [112,113]. The frequency of coexisting taste impairment was found higher in patient without DM than in diabetics, suggesting the location of the lesion might differ [107]. Diabetic patients with Bell's palsy had a slower recovery and had a lower facial movement score than patients without DM [114]. It has been reported that only 25% of the patients achieved normal facial muscle function, unlike 70% of nondiabetic patients [115]. On the contrary, in other studies the prognosis of facial nerve palsy of patients with and without DM did not differ [111,116].

Facial neuropathy was also described in patients with DM. Its real incidence is unknown because it is difficult to clinically distinguish it from Bell's palsy [117,118]. There is evidence that the facial nerve is sub clinically defected in 6% of patients with DM [119,120]. Other cranial neuropathies are considered to coexist in patients with DM and facial nerve palsy [121]. Development of facial neuropathy could be attributed to ischemic and inflammatory changes secondary to DM [4]. A few case reports described pathological nerve findings in temporal bones of diabetic facial nerve with neuropathy [122,123]. Furthermore, blood vessel walls in the facial nerve canal were found significantly thicker in diabetic patients than in those without DM [124]. These finding imply that diabetic complications including diabetic neuropathy can make diabetic patients more susceptible to facial nerve palsy and impair recovery.

Secondary peripheral facial nerve paralysis is defined as secondary to a detectable cause. There are several possible etiologies that are more frequent among patients with DM. Mucormycosis, a severe mycotic infection of the paranasal sinuses and surroundings, can cause facial nerve paralysis in conjunction with rhino-cerebral mucormycosis in 11% of cases [125]. Another cause is malignant otitis externa, an infection of the external auditory canal that spreads to the temporal bone and skull base, most commonly to the stylomastoid foramen and injures the facial nerve [23–25]. Parotid abscess is also more common among patients with DM and can cause perineuritis secondary to nerve compression and the toxic effect of the surrounding inflammation [126].

6. Olfactory dysfunction

Olfaction is an essential component of overall quality of life and personal safety. Chemosensory function has been previously assessed in patients with diabetes mellitus [8,127–135]. Pathogenesis and clinical significance remain unclear. Some researchers describe poor performance of diabetics in olfactory testing [8,127–130] while others report normal scores [131–135]. No correlation was found between olfactory function and the duration of the disease or HbA1c levels [8,127,128,131,136,137]. Olfactory impairment is considered as a form of cranial mononeuropathy, an uncommon phenomenon known to occur in the elderly and in patients with prolonged duration of diabetes [138]. Diabetic peripheral neuropathy and neuropathic pain were found in association with olfactory dysfunction, suggesting preceding chronic ischemia and demyelination due to vascular damage [137,139]. Other forms of microvascular disease, such a diabetic retinopathy and nephropathy were also found in association with olfactory dysfunction [8,136,140].

Diabetic patients often suffer from comorbidities. It has been previously suggested that diabetic patients who suffer from other medical conditions such as hepatic or renal failure, cardiovascular disease, cognitive decline, depression and hypothyroidism have increased risk for isolated olfactory dysfunction independent of glycemic control [128,134,139].

Olfactory dysfunction is often overlooked and untreated. A recently published trial showed that hyperbaric oxygen treatment of patients with diabetic neuropathy and olfactory dysfunction led to a significant improvement in olfaction [129].

7. Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is a common condition characterized by inflammation of the nasal mucosa and paranasal sinuses for at least 12 weeks [141]. DM patients have increased risk for skin and mucous membrane infections [142]. Even though, the incidence of DM among patients with CRS is actually lower that the incidence of DM in general population (4.2–5% Vs. 8.3%) [143]. The symptoms and quality for life, as measured by the SNOT-22 and RSDI instruments, were found similar among age and Lund-Mackay scores matched patients with CRS, with or without DM [144].

The most common bacteria isolated from sinuses of patients with CRS are *Pseudomonas aeruginosa* and Staphylococcus aureus [145]. Patients with DM and CRS were found more likely to arbor other gram negative rods in addition to Pseudomonas [6]. In a single study, CRS patients with DM where significantly more likely to have nasal polyps compared to non-diabetic patients [143]. These patients had a higher incidence of gastroesophageal reflux disease (GERD), a recognized risk factor for CRS [143,146]. GERD was found especially common in diabetic patients with diabetic neuropathy [147].

Osteomyelitis is a rare complication of CRS, most commonly in the frontal bone, rarely the maxilla is involved [148–150], the risk is increased in DM patients [151]. It was reported that 15% of patients with frontal bone oseomyelitis secondary to CRS had co-existing diabetes [149]. In another study, 68% of maxillary osteomyelitis

cases had DM [148].

Endoscopic sinus surgery (ESS) is a well-established modality in treating recalcitrant CRS. It is known to relief symptoms, improve quality of life and offers better endoscopic appearance after surgery [152–154]. Surgical outcomes of patients with diabetes were similar to that of patients without DM. Patients experienced similar benefit at a 12 month follow-up assessment [155,156]. A similar degree of improvement was reported by patients with or without DM, using SNOT-22, 1 and 3 month postoperatively but not at 6 month [143]. Among diabetic patients, insulin treatment was not correlated with adverse surgical outcomes [144].

8. Fungal sinusitis

Acute invasive fungal rinosinusitis (AIFR) is a rare and aggressive infection [157,158]. It is often fatal, mortality rate is up to 80% [159,160]. It occurs most commonly in immunocompromised patients and in patients with poorly controlled diabetes mellitus [12,161,162]. AIFR is characterized by invasion of fungus into mucosa, submucosa and blood vessels of the nose, paranasal sinuses and surrounding structures including the orbit, cavernous sinus and brain parenchyma [163]. Blood vessels invasion results in thrombosis, hemorrhage, tissue infarction and necrosis [164]. The typical species responsible for the invasive infections are Zygomycetes species (*Mucor, Rhizopus*)and *Aspergillus* [165]. Mucormycosis occurs more frequently in patients with diabetes [166]. The fungus has an active reductase system that permits its thriving in an acidic and hyperglycemic environment. Furthermore, the acidic serum causes iron dissociation from transfertin so it is available for fungus replication [158]. Hyperglycemia also alters the glutathione pathway and impairs phagocytic capabilities, allowing fungus survival [167].

Rhinocerebral mucormycosis (RCM) is the most common form of mucor infection among patients with unballanced diabetes. 60–81% of patients with RCM have DM [158,168–170]. The infection usually originates from nasal cavity, spreads to paranasal sinuses (especially to ethmoid and maxillary sinuses) and orbit producing facial and orbital pain, visual loss and swelling [163,171,172]. Dark nasal discharge is typical, with black necrotic areas seen in the turbinates and nasal septum [173,174]. Sloughing of the hard palate, orbital cellulitis, ophthalmoplegia, proptosis and loss of vision may also occur [157,171]. The pterygopalatine fossa is usually infected and constituted the main reservoir of the fungus. The organism spreads along nerves, the cribriform plate, orbit and ophthalmic artery to the meninges and brain. Fungal vascular invasion leads to infarction and necrosis of the brain and death most likely follows [172].

Once diagnosis is made, prompt aggressive surgical detriment and antifungal therapy is mandatory. Tight glycemic control is very important for successful treatment. Diabetes is more manageable condition than other predisposing morbidities such as hematologic malignancies [175,176]. While some studies report DM is a poor prognostic factor [162,177,178], most describe favorable survival rates in diabetic patients [169–176,176–181]. Survival rate as high as 70–89% survival rate was reported in diabetic patients [179,180]. This could be associated with the improvement of glycemic control.

Chronic invasive fungal sinusitis (CIFS) is another rare mycotic paranasal sinuses disease. Histopathologically appearance is characterized by fungal tissue invasion with non-granulomatous inflammation. Unlike AIFS, the onset of the disease is usually slow and insidious and a the course of disease is more indolent. Similarly to AIFS, diabetes mellitus is a predisposing factor. Infection usually affects the ethmoid sinuses and may extend into the orbit. Orbital apex syndrome, a characteristic impairment of several cranial nerves, is a common clinical presentation. Treatment is the same as for AIFS, focuses on surgery and antifungal medication [182].

9. Laryngeal manifastations

The Larynx main functions are airway protection and phonation. Malfunction may develop in DM probably as a result of diabetic immunosuppression and diabetic microvascuar and macrovascualr damage [183]. These are responsible for increased incidence and severity of infections such as laryngeal candidiasis and epiglotitis [15,184,185]. Furthermore, the susceptibility to laryngeal injury after endotracheal intubation is increased in diabetics [16]. Impaired immunity and compromised blood supply may contribute to the development of subglotic and laryngotracheal stenosis [186,187].

A greater incidence of surgery independent vocal cord palsy (VCP) has been reported in diabetic patients in comparison with nondiabetic [188–192]. Moreover, diabetics have increased risk of VCP following endotracheal intubation [193]. Both unilateral and bilateral VCP were associated with DM [188–192]. On the contrary, the risk of postoperative VCP, a well-known sequela of thyroid surgery, was not increased in diabetic patients [194]. Even though, electrophysiological studies of the recurrent laryngeal nerve revealed functional defect, suggesting nerve injury susceptibility in diabetics [195,196]. These findings imply that the vagus and recurrent laryngeal nerves are affected by diabetic neuropathy similarly to peripheral nerves [188,190].

A single study evaluated voice characteristics of patients with DM. Perceptual evaluation of voice quality using GRABS classification produced slightly higher scores for patients with DM than for healthy controls. The difference was exaggerated in poor glycemic controlled diabetic patients and in patients with diabetic neuropathy. Furthermore, diabetic patients had decreased maximum phonation time compared with controls [197].

Voice production requires breathing oscillation and resonance. Compromised function of one of these components may affect voice. Diabetic myopathy is a known complication of long standing poorly controlled DM [198]. It has been suggested, but not proved, that myopathy of laryngeal muscles and respiratory muscles may affect voice production [197]. In addition, diabetic neuropathy of vagus and recurrent laryngeal nerve contribute to impaired phonation [199].

Patients with diabetes are prone to gastroesophageal reflux disease (GERD) [200,201]. The incidence of GERD is increased with poorer glycemic control, microvascular complications and longer DM duration [202]. Furthermore, the incidence of ancillary disease, such as Barrett's esophagus and esophageal adenocarcinoma is higher in diabetics [203,204]. GERD symptoms may be atypical in diabetics which obscures the diagnosis. Cough and hoarseness are more prominent symptoms in diabetics, while chest pain and dysphagia may be vogue [205]. The pathophysiology of GERD in diabetics could be attributed to autonomic neuropathy responsible for esophageal dysmotility and gastroparesis [206–209].

10. Salivary gland dysfunction

Salivary function is essential for maintaining oral health. Saliva protects and maintains the integrity of the oral mucous membrane by lubrication and soft tissue repair. Saliva has direct antibacterial, antiviral and antifungal activities. The buffer capacity of saliva is crucial of maintaining optimal oral pH and tooth integrity [210]. Impaired salivary flow rate and altered composition of saliva may predispose to caries, periodontal disease, oral mucosal lesions and infections [210–212].

Salivary gland hypofunction has been well documented in DM

patients [213–215]. Saliva production in diabetics is compromised due to diminished extracellular fluid secondary to hyperglycemia induced diuresis [216,217]. Furthermore, persistent hyperglycemia may cause microvascular alterations, autonomic neuropathy and structural changes in the salivary glands, leading to functional deteriorating [214,217].

Salivary flow rates were significantly reduced in diabetics in several studied [213]. Moreover, chemical properties of saliva were altered: increased protein concentration was found [213,218]. Salivary proteins such as α2-MG, α1-antitrypsin, alpha amylase, lactoferrin and chalone C were found in higher concentration in DM patients [216,219–221]. However, a reduced concentrations of several other specific proteins, such as proline-rich protein and statherin was observed [222,223]. Saliva pH is lower in diabetics, acidity degree of saliva correlates with poor glycemic control [215,217].

Xerostomia, is the subjective sensation of a dry mouth. Diabetic patients are inclined to suffer from xerostomia, with a reported prevalence of 14–62% [224,225]. Xerostomia can be secondary to thirst, dehydration, oral sensory dysfunction and hyposalivation [226]. Although a dry mouth sensation may be associated with DM, it is not a valid indicator of glandular dysfunction.

Altered saliva composition and quantity and impaired immunity may predispose to salivary gland infections [227,228]. Parotid gland infections in diabetics are often more severe, with a higher rate of abscess formation and neck extension. Diabetic patients, especially poorly glycemic controlled, suffer from greater morbidity including higher rates of facial nerve palsies, septicemia and death. The bacteria associated with salivary glands infections in diabetics differ, Klebsiela pneumonia is more commonly isolated [229].

Sialadenosis (sialosis) is an asymptomatic bilateral parotid gland enlargement [230]. It is relatively common among diabetics, with a reported prevalence ranging from 10% to 80% [231]. Occasionally, submandibular glands are involved and only rarely minor salivary glands [231–233]. This condition is apparently preceded by autonomic neuropathy, leading to dysregulation of protein synthesis and saliva secretion of the gland [20]. Cytoplasmic swelling is the result of cellular engorgement by intracytoplasmic granules. As a result, the parotid's acini become enlarged [234,235]. The parotid parenchymal hypertrophy may replace existing normal intraparotid fat [234]. Sialadenosis can also result from fat infiltration of the gland which is probably secondary to a local lipid metabolism disorder. Fat replacement of acinar cells leads to salivary production insuficiency [217,236,237].

11. Deep neck infections

Deep neck infections occur in potential spaces in the neck bound by cervical fascia. They spread along fascial planes and may escalate quickly [238]. Diabetic patients have an increased susceptibility to deep neck infections. Studies suggest that diabetic patients have more frequent infections, they are older and have more severe infections with a higher rate of complications, which require prolonged hospitalization and more aggressive therapy [239–243]. Deep neck infections in diabetics are seen more often in the upper cervical region [239]. Many cases have unclear primary region of infection and extensive inflammation that tends to spread outwards [243–245]. Additionally, infections in diabetic patients may be populated with different bacterial flora, making culture and sensitivity data essential for management [241,242].

12. Head and neck cancer

An increased body of evidence suggests certain types of cancer are more common in DM patients. Previous studies reported increased risk of cancers of liver, pancreas, colon, breast, endometrium and stomach [245–253]. A possible association between head and neck cancer and DM has been considered [254–260]. However, there are discrepancies regarding the risk of head and neck cancer in patients with DM [255,258,260,261]. Several researches demonstrated diabetics have an increased risk of laryngeal, pharyngeal, nasopharyngeal and oral cavity cancer [254–260]. Moreover, a strong association between well differentiated thyroid carcinoma and DM was found [262]. The diabetic carcinogenic effect can be related to insulin resistance,hyperinsulinemia, increased level of serum IGFs (Insulin growth factors), abnormal carbohydrate and lipid metabolism and chronic inflammation [246,263–266].

The impact of DM on the prognosis of head and neck cancers has been studied and revealed unfavourable overall survival of DM patient with head and neck squamous cell carcinoma [267]. Often, head and neck cancer patients require major neck surgery with increased risk of major complications after surgery [267–269]. Wound complications such as wound infection and fistula formation are more common in diabetics [269,270]. In reconstructive microsurgery, DM is related to increased risk of postoperative complications and free flap failure [259,271–273]. Hospitalization after major head and neck surgery is usually longer and more expansive [269,274]. Postoperative complications such as cardiac manifestations, respiratory compromise and acute renal failure are more common in diabetics [269,275]. Additionally, postsurgical stroke was found more common after neck dissection in diabetics [276]. Overall, DM has a significant impact on mortality of head and neck cancer patients [277,278].

Metformin, the most common oral hypoglycemic drug, is known to inhibit cell proliferation [246,264]. It is related to decreased risk of several cancers, including liver, lung and prostate [279,280]. The protective effect of metformin treatment on head and neck cancer was observed in several studies [281,282], though the effect was not consistent in all [283]. An improved outcome of Metformin treated diabetic head and neck cancer patients was suggested [284]. Metformin treated patients had decreased rates of locoregional recurrence and neck metastasis and improved overall survival compared to patients not treated by Metformin [281,285–287]. However, in another study Metformin treatment did not affect survival [287]. Metformin has been shown to potentiate the effects of radiation therapy, but have no effect of the propensity of distant metastasis [288,289]. The protective effect of Metformin treatment can be explained by its role in the activation of adenosine monophosphate-activated protein kinase (AMPK), that inhibits mTOR protein action and decreases cell proliferation [280,290].

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