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THE ASSOCIATION BETWEEN MALIGNANT OTITIS EXTERNA AND DIABETES MELLITUS : A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Diabetes mellitus is one of the risk factors for malignant otitis externa. There are very few studies on the disease and there is a need to pool the prior studies to highlight the characteristics of the disease.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 177 articles, whereas the results of our search on SagePub brought up 56 articles. The results of the search conducted for the last year of 2013 yielded a total 59 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 4 papers, 3 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.*

Conclusion: *MEO is an aggressive type of external otitis leading to osteomyelitis of the skull base bone. The usual microorganism involved is Pseudomonas species, and it usually affects individuals with diabetes mellitus. Treatment of the disease has changed over the years, today following conservative treatment modalities with antibiotics and conducting surgery under special circumstances. MEO is a rare but fatal disease, and the specialists involved in its diagnosis and treatment, namely ENT surgeons and diabetes specialists, should be aware of it.*

Keyword: *Malignant otitis externa, diabetes mellitus*

INTRODUCTION

Malignant external otitis (MEO)—or malignant otitis externa or necrotizing external otitis—is an aggressive type of external otitis which shows an outspread of inflammatory activity towards the soft tissues of the external auditory meatus and bone of the skull base and presents severe morbidity and mortality. Use of the term malignant is unsuitable, since it does not describe the development of cancer but more the rapid local spread of the inflammation to healthy tissues. The first report of the disease is attributed to Toulmouche in 1838, while the term 'malignant otitis externa' was first used by Chandler in 1968.[1]

Malignant (necrotizing) external otitis (also termed malignant otitis externa) is an invasive infection of the external auditory canal and skull base, which typically occurs in older adult patients with diabetes mellitus. Increasing reports of malignant external otitis in patients infected with the human immunodeficiency virus (HIV) implicate a compromised immune system as a predisposing factor in this disease. *Pseudomonas aeruginosa* is nearly always the responsible organism. The widespread use of oral and topical fluoroquinolones for the treatment of otitis may make the isolation of *P. aeruginosa* more difficult and has contributed to the emergence of *P. aeruginosa* resistant to ciprofloxacin.[2]

Malignant external otitis (MEO) or necrotising otitis is a rare entity, the starting point is a violation of the external ear canal (EEA) and dissemination of the infection to the soft parts and the adjacent bone, hard adiagnostiquer and whose evolution can be very serious. Elective on debilite ground, such as immunocompromised, or more often the elderly diabetic, is a necessary diagnostic criterion. The symptoms and signs may include severe earache, otorrhoea and achievement of various crannies, often caused by Pseudomonas Aeruginosamais also of other agents can rarementinclure to other bacteria (Staphylococcus aureus, Proteusmirabilis, Klebsiellaoxytoca, Pseudomonascepacia) or fungi (Aspergillus, Pseudallescheria, Candida, Pityrosporum).[3]

In 2016, the prevalence of diabetes among adults aged 30 years and older was 14.4%. Diabetes is known to lead to chronic diseases, including chronic kidney disease (CKD) and retinopathy, and diabetes have an increased risk of infection. Among diabetes, poor glycemic control increases the risk of infection, diabetes neuropathy, and impaired innate and adaptive immune responses. Population-based cohort studies conducted in Europe and the United States have found that the incidence of infectious diseases and hospitalization was higher in diabetes than in the general population.[4,5]

Despite the advances in the treatment of MEO, incidence rates of 10–20% have been published, with a more recent study from the US reporting an overall mortality of 2.5% during the initial hospitalization. Existing diabetes and poor glycemic control are associated with longer hospitalization, increased healthcare costs and mortality in this patient category.[1]

It is so very important to make the diagnosis of MEO as soon as possible, at the beginning it is very similar to severe acute external otitis, but MEO is developing a severe osteomyelitis of the temporal bone, attaquantles cranial nerves adjacent (VII, XII), the blood vessels and soft tissue, and finally, if it is not treated, it causes death due to the expansion osteomyelite of the skull and thrombo-embolism septic disseminated brain. Therapy should be should be conducted by the otolaryngologists in collaboration with the endocrinologist, internist, neurologist, radiologist and microbiologist. Local treatment (with removal of bone sequestered) and systemic antibiotic treatment according to the results of bacteriological tests (aminoglycosides, semisynthetic Penicillins, third- and fourth-generation cephalosporins, fluoroquinolones) are generally accepted.[3]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review the association between malignant otitis externa and diabetes mellitus. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "otitis externa" and "diabetes mellitus" as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("malign"[All Fields] OR "malignance"[All Fields] OR "malignances"[All Fields] OR "malignant"[All Fields] OR "malignants"[All Fields] OR "malignities"[All Fields] OR "malignity"[All Fields] OR "malignization"[All Fields] OR "malignized"[All Fields] OR "maligns"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancies"[All Fields] OR "malignancy"[All Fields]) AND ("otitis externa"[MeSH Terms] OR ("otitis"[All Fields] AND "externa"[All Fields]) OR "otitis externa"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields])) AND ((clinicaltrial[Filter]) AND (2013:2023/12/12[pdat]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

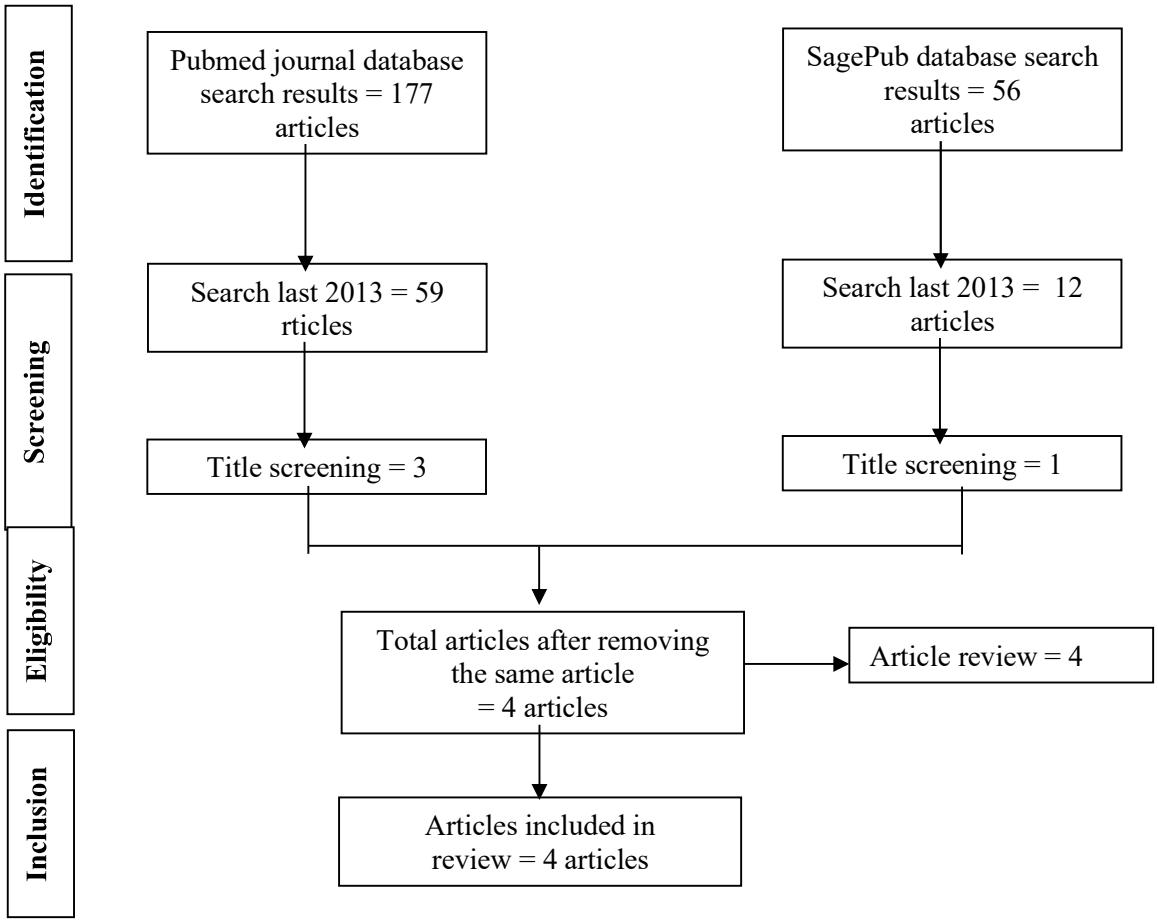

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised

in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 177 articles, whereas the results of our search on SagePub brought up 56 articles. The results of the search conducted for the last year of 2013 yielded a total 59 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 4 papers, 3 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Yang, et al[6] (2020) showed that there is an association between MOE and diabetes. One clinical practice implication of our study is that when a patient with diabetes complains of otalgia or otorrhea, and physical examination shows swelling of the ear canal or granulation growth, physicians should consider the possibility of MOE.

Peled, et al[7] (2022) showed that HbA1c at admission is associated with longer hospitalization duration among NOE patients. Mean blood glucose during hospitalization was associated with a higher likelihood of PA infection, however, it had no effect on disease outcome.

Habra, et al[3] (2018) showed that the occurrence or severity of MEO is not correlated to the imbalance of diabetes, however this imbalance. Bacteriological examination and the antibiogram and medical imaging should be systematic, after confirming diagnosis, adequate treatment avoiding the basicranienne extension. This became almost exclusively medical with the appearance of antipyocyaniques antibiotics which have transformed the once formidable prognosis. Stop antibiotic therapy is conditioned by the standardization of the scan to the Galliu, an optimized insulin therapy is fundamental. The overall mortality is less than 20 percent today. Malignant external otitis or external otitis progressive Necrotizing is a serious infection of the subject the often older and diabetic by Pseudomonas aeruginosa. There are prevention by avoiding all the traumatic maneuvers of the EEC, and especially think about in order to establish as early as possible after confirmation diagnostic.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Yang et al, 2020[6]	Taiwan	Cross Sectional	728 patients	In total, 728 (24.2%) out of 3 012 sample patients had diabetes prior to the index date. Chi-square test revealed a significant difference in diabetes prevalence among cases and controls (54.8% vs 13.9%, $p <$ 0.001). Simple logistic regression showed the odds ratio for prior diabetes among cases versus controls was 7.50 (95% CI, 6.22~9.03). The adjusted odds ratio of prior diabetes for cases versus controls was 10.07 (95% CI, 8.15~12.44) after adjusting for patient demographics and medical co-morbidities.
Peled et al, 2022[7]	USA	Retrospective study	Patients hospitalized 1990-2018	Eighty-nine patients were included in the study. Eighty-three patients (94.3%) had DM. Preadmission HbA1c was 8.13% (5.8-12.6%). Forty-nine patients (65.5%) had mean blood glucose of ≥ 140 mg/dL and 26 (34.5%) had ≤ 140 mg/dL. DM duration was 157.88 months among NOE patients who required surgery, and 127.6 months among patients who were treated conservatively (p value 0.25).

				HbA1c in patients hospitalized < 20 days was 7.6%, and 8.7% among NOE hospitalized ≥ 20 days (p value 0.027). Seven patients with mean blood glucose of ≤ 140 mg/dL had Pseudomonas Aeruginosa (PA-NOE) (26.7%), in comparison to 25 (51.0%) with mean blood glucose measurement of ≥ 140 mg/dL (p = 0.045).
Habra et al, 2018[3]	Morocco	Retrospective study	12 patients	All of patients had an MEO manifested by a discreet, banal, earache that gradually will intensify, be accompanied by a variable but typically festering abundance otorrhoea. The average age of patients was 70 years. Seniority of diabetes was 9 years at 90%. It is essentially type 2 diabetes imbalanced (70.5%). There is a fickle hearing loss and moderate at 35.3%. Facial paralysis full at 58.8% of the patients. The more found germ is Pseudomonas aeruginosa (90%). Antibiotic therapy adapted to the antibiogram is prescribed, with intensified insulin therapy. The predisposed field is essentially diabetes (75 to 95% of the cases in large series of literature).
Guerrero-Espejo et al, 2017[8]	Spain	Retrospective study	355	A total of 355 patients (302 as principal diagnosis and 53 as secondary) were diagnosed. The incidence rate was 1.30 (95% CI, 1.17 to 1.44) per 106 inhabitants and year, although there were variations among geographical areas. The median age of cases with main diagnosis was 74 years (range 10-95 years). The predominant age group was in patients over 84 years old (19.3 cases per 10^6 inhabitants and year). The incidence was higher in men and the male-female relative risk was 2.4. Diabetes was present in 74.6% of patients. The diagnosis was predominant in the last quarter of the year. The gross in-hospital mortality rate was 3.7%.

Guerrero-Espejo, et al[8] (2017) showed that there is an association between diabetes mellitus and malignant otitis externa with74.6% of patients with MEO had diabetes, while the disease predominantly affected patients > 84 years of age.

DISCUSSION

Malignant otitis externa (MOE) is a relatively rare complication of Otitis externa with a tendency to spread to other parts of temporal bone and skull base. Pseudomonas aeruginosa is the most common pathological agent. It generally occurs in the elderly with poorly controlled diabetes. In this report we present a case of MOE with atypical initial presentation causing immense conundrum in deciphering the diagnosis early.[9]

As implied by its name, the disease is believed to originate from the external acoustic meatus and can evolve from cellulitis to chondritis, periostitis and eventually osteomyelitis, thus involving the bone of the skull base and the cranial nerves arising from the skull base foramens. Therefore, the term 'skull base osteomyelitis' is also used in its final stages.(Shamanna) MEO progresses from the external auditory meatus through the fissures of Santorini and then through fascial and vascular planes and can reach the dural sinuses and petrous apex. Except for the stylomastoid foramen and the facial nerve, which can be affected, the disease can also reach the jugular foramen and thus the vagus, glossopharyngeal and accessory nerves. The inflammation can reach the hypoglossal canal and nerve and finally the cavernous sinus with its structures.[10]

Pseudomonas aeruginosa is predominantly involved in cases of MEO with a frequency of 50–90% of all cases. *Proteus mirabilis* and other *Proteus* species, *Staphylococcus epidermidis* and *Klebsiella species* are also commonly implicated bacteria. Fungi, such as Aspergillus fumigatus and Candida species have also been isolated in cultures. Methicillin-resistant Staphylococcus aureus (MRSA) should also be suspected in patients without diabetes. During the last years, however, an increase in culture-negative patients has been reported. This could be a result of modern treatment protocols, which demand an immediate prescription of antibiotics upon patient presentation rather than a shift in the involved bacteria.[11]

MEO and advanced age have been traditionally linked to elderly patients with diabetes. Another patient group at higher risk of MEO is those with immunodeficiencies, such as patients with human immunodeficiency virus (HIV) or cancer. In these patients the symptoms of inflammation are suppressed.. A high index of suspicion should be held concerning immunodeficient individuals with external otitis not responding to antibiotics. Radiation therapy of the head and neck area has also been linked to MEO, through chronic inflammation and necrosis of the soft tissues and bone.[12]

MEO most commonly presents with non-resolving nocturnal ear pain, followed by exudate, hearing impairment and temporomandibular joint. Otoscopic findings include edema of the external ear canal with granulation tissue at the osseocartilaginous junction and more rarely only edema or aural polyps. Palsies of the cranial nerves on the side of MEO are not unusual. Clinical evaluation should include examination of the cranial nerves, specifically the facial (VII), glossopharyngeal (IX), vagus (X), accessory (XI) and hypoglossal (XII) nerves. The facial nerve is most commonly while the hypoglossal nerve most rarely affected. It has been reported that facial nerve paralysis increases mortality by 50%. Facial nerve paralysis is considered to occur in 75% of individuals with *Aspergillus* infection, while only in 34% of those with *Pseudomonas* infection.[1]

It is very important to diagnose the disease in the early stages, because it progresses and spreads over time, greatly affecting the skull base with high morbidity and mortality. Therefore, family physicians treating patients with external otitis should be suspicious of MEO when nocturnal pain and symptoms persist despite treatment with antibiotics and when granulation tissue of the external auditory meatus is present. A bacterial culture should be obtained before prescription of antibiotic agents, and the patient should be referred to an ENT surgeon if the symptomatology persists for more than a week.[1]

According to a systematic review, hyperbaric oxygen therapy could be a significant adjunct in the treatment of refractory or chronic cases of MEO, particularly in patients with diabetes mellitus. As already mentioned, patients with diabetes exhibit significant factors that contribute to MEO development like poor white blood cell chemotaxis and diabetic microangiopathy, which lead to tissue hypoxia. Hyperbaric oxygen therapy, on the other hand, is considered to ameliorate oxygen partial pressure in the site of infection, increase bone and soft tissue healing and improve oxygen-mediated leucocyte function.[13]

Different complications of MEO should receive more targeted treatment. For example, temporomandibular joint inflammation, which is rare and considered to have poor prognosis, can be treated with skeletal muscle relaxants for symptom relief. Facial nerve palsy as an indication for surgery is debatable, since according to several authors, many cases are associated with good response to conservative treatment. Thus, it is important to evaluate the overall clinical picture of the patient. Overall, use of classification systems, e.g., the Peleg score, to classify patients as non-severe and severe could be implemented to decide proper treatment. Non-severe patients can be treated mainly with antibiotics and minimal surgery of the external acoustic meatus when needed. Severe patients should receive an aggressive therapy with multiple antipseudomonal antibiotics and early surgical debridement of the affected structures.[14]

As already mentioned, patients with diabetes are at risk of MEO. This specific group presents microangiopathic changes in the external auditory meatus and hindering of the white blood cell chemotaxis, which leads to vulnerability to infections. Specifically, in a study by Guerrero-Espejo et al., 74.6% of patients with MEO had diabetes, while the disease predominantly affected patients > 84 years of age.(Guerrero-Espejo) In a population-based case control study by Yang et al., patients with MEO had a prevalence of diabetes mellitus of 54.8% and an adjusted odds ratio of diabetes for patients with MEO versus controls of 10.07 (95% CI).[6]

Hyperglycemia and glucose variability in hospitalized patients with and without diabetes are linked to a notable increase in morbidity, mortality and health-care costs. Insulin therapy is recommended as the cornerstone of inpatient pharmacological treatment of MEO. Most clinical guidelines recommend stopping oral antidiabetic drugs during hospitalization. However, continuation of oral glucose-lowering medications is applied in some hospitalized patients in different countries. This is based on a variety of clinical trials that suggest that non-insulin antidiabetic agents, alone or in combination with basal insulin, can be used to achieve efficient glycemic control in selected populations. In stable patients who are adequately controlled on their outpatient regimen and are able to eat, oral agents may be continued.[15]

A plethora of treatment options for diabetes exist. Modifications to diet or medication regimens may be used to improve high blood glucose level. Basal insulin or a basal plus bolus insulin correction regimen is the preferred treatment for noncritically ill hospitalized patients with inadequate oral intake. An insulin regimen including basal, prandial and correction components is the preferred choice for patients with sufficient nutritional intake. Insulin therapy should be initiated for the treatment of persistent hyperglycemia at the level of ≥ 180 mg/dl (10.0 mmol/l, confirmed on two occasions), targeting a glucose range of 140–180 mg/dl (7.8–10.0 mmol/l) for most critically ill and hospitalized patients. In the critical care setting, continuous intravenous insulin infusion is the best option for adequate glycemic control. Before intensive care unit discharge, stable patients can be transitioned to subcutaneous insulin regimens.

MEO, although rarer, presents similarities to the pathogenesis of and population involved in diabetic foot osteomyelitis. Specifically, microangiopathy and neuropathy are considered to play a key role in both. It is interesting to remember, however, that MEO is usually monomicrobial, while diabetic foot osteomyelitis is polymicrobial, and that an ear swab culture usually suffices for MEO, while in the latter bone biopsy is needed for diagnosis.

CONCLUSION

MEO is an aggressive type of external otitis leading to osteomyelitis of the skull base bone. The usual microorganism involved is *Pseudomonas* species, and it usually affects individuals with diabetes mellitus. Treatment of the disease has changed over the years, today following conservative treatment modalities with antibiotics and conducting surgery under special circumstances. MEO is a rare but fatal disease, and the specialists involved in its diagnosis and treatment, namely ENT surgeons and diabetes specialists, should be aware of it.

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