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Association between type 2 diabetes mellitus and multiple myeloma: Fact or fiction

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ABSTRACT

Multiple myeloma is a plasma cell cancer causing bone and marrow damage, resulting in hypercalcemia, anemia, and renal insufficiency. Diabetes mellitus occurs in 6-24% of multiple myeloma cases, associated with immunosuppression, inflammation, and lymphocyte dysfunction, possibly contributing to multiple myeloma development. Insulin and insulin-like growth factor-1 also contribute to multiple myeloma pathogenesis. The incidence of both multiple myeloma and diabetes mellitus is expected to rise due to the aging population, lifestyle changes, genetic predisposition, and improved diagnostic methods. Although the link between diabetes mellitus and hematological malignancy risk is less conclusive, insulin resistance and growth factors may promote tumor cell proliferation. Genetic variants linked to type 2 diabetes mellitus (T2DM) influence multiple myeloma risks. The insulin like growth factor 1 (IGF1) gene triggers malignant plasma cell proliferation. Additionally, poorly managed T2DM-induced acidosis creates a favorable environment for cancer cell growth, including multiple myeloma. T2DM and metabolic syndrome (MetS) increase multiple myeloma risks through insulin resistance, hyperinsulinemia, inflammation, and dyslipidemia. Inflammatory cytokines [interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-1β (IL-1β)] contribute to insulin resistance, chronic inflammation, and multiple myeloma cell survival too. The coexistence of diabetes and multiple myeloma presents challenges in managing complications like neuropathy, nephropathy, and retinopathy. In conclusion, the association between T2DM and multiple myeloma has been established, with a discernible influence from distinct genetic variations. Notably, IL-6, TNF-alpha, and IL-1β exert significant influence on the development of insulin resistance and the proliferation of cancer cells, and also their viability. Consequently, the involvement of inflammatory cytokines, dyslipidemia, and IGF1 in the progression of MM among patients with T2DM and MetS is noteworthy.

Implication for health policy/practice/research/medical education:
According to our comprehensive review, there exists a correlation between T2DM and the onset and advancement of multiple myeloma, which can be attributed to a variety of distinct mechanisms.

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Review

Introduction

Multiple myeloma is a malignant condition that originates in plasma cells, which are a type of white blood cell responsible for producing antibodies that disrupt bone health and bone marrow function, leading to an array of clinical presentations, such as hypercalcemia, anemia, and renal insufficiency (1). Reports suggest that diabetes mellitus is a complication in 6%-24% of multiple myeloma cases (2,3). Diabetes mellitus is a metabolic disorder characterized by high blood glucose levels that can occur due to insulin deficiency or the impaired ability of the body to use insulin (4). Diabetes mellitus is associated with immunosuppression, chronic inflammation, and lymphocyte dysfunction, all of which are recognized to play a role in the development of multiple myeloma (5). In addition, Insulin and insulin-like growth factor-1 are also believed to play significant roles in the pathogenesis of multiple myeloma by promoting the growth and survival of tumor cells (6).

Multiple myeloma comprises 1.3% of all cancer cases and 10-15% of hematological neoplasms, with the greatest incidence rates noted in affluent nations (7). Sociodemographic factors contribute to the variability in multiple myeloma incidence rates, with a ten-fold difference observed between countries with the lowest and highest occurrence rates (8). Multiple myeloma's prognosis remains unfavorable, with an overall survival rate of no more than 55% over five years (9). Age, male gender, African ancestry, and monoclonal gammopathy of uncertain significance (MGUS) have been established as major risk factors for multiple myeloma (10). With the prevalence of type 2 diabetes mellitus (T2DM) on the rise globally, an increase in the number of cases diagnosed with both multiple myeloma and diabetes mellitus is anticipated (1).

Based on the epidemiological evidence, diabetes has been associated with a higher incidence of various cancers, such as pancreatic, liver, colon, breast, and endometrial cancer (1). However, studies regarding the link between diabetes and the risk of hematological malignancy are less conclusive (1). This association is thought to be related to insulin resistance, which is a precursor to T2DM and insulin-like growth factors (11). Both of these factors have been shown to promote tumor cell proliferation in laboratory experiments (10). Numerous studies have reported an increased cancer risk in patients with diabetes. For instance, in a phase 3 APEX trial that involved individuals with relapsed multiple myeloma, 18% of the participants (n= 331) had either a baseline glycosylated hemoglobin level above the normal upper limit or a history of diabetes (1).

Previous studies on the relationship between T2DM and multiple myeloma have yielded inconsistent results, possibly due to differences in study design and population characteristics (12). This study aims to provide a more definitive understanding through a comprehensive search, with implications for future research and clinical practice.

Search strategy

In this study, a comprehensive search for relevant studies was conducted using various databases, including PubMed, EMBASE, Scopus, and DOAJ, up to April 21, 2023. Specific keywords such as "type 2 diabetes mellitus," "multiple myeloma," "hematological malignancy," "therapy," "acidity," "genetic variants," and "metabolic syndrome" were used to perform the search. The inclusion criteria consisted of clinical trials, systematic reviews, and retrospective and prospective studies exploring the association between diabetes and multiple myeloma. Studies written in languages other than English were excluded. The abstracts of all studies were reviewed by three authors, and the selected studies were qualitatively analyzed.

Type 2 diabetes-associated genetic variants and multiple myeloma risks

Several studies have established a link between genetic variations associated with T2DM and the risk of developing multiple myeloma (10,13,14). Certain genotypes, such as KCNQ1rs2237892T, CDKN2A-2Brs2383208G/G, IGF1rs35767T/T, and MADDrs7944584T/T, were found to increase the risk of multiple myeloma, while other genotypes, such as KCNJ11rs5215C, KCNJ11rs5219T, THADArs7578597C alleles, FTOrs8050136A/A, and LTArs1041981C/C, were associated with a decreased risk of multiple myeloma (Table 1) (10). Interestingly, the direction of association between these genetic variants and multiple myeloma was opposite to that of genome-wide association studies (GWAS) for T2DM, which suggests a non-diabetic mechanism responsible for the effects of these variants on multiple myeloma risk (10).

Further studies have shown that some of these genetic

Table 1. type 2 diabetes-associated genetic variants

Increase the risk of MM		Decrease the risk of MM	
Gene name	**dbSNP rs#**	**Gene name**	**dbSNP rs#**
CDKN2A-2B	rs2383208	FTO	rs8050136
IGF1	rs35767	KCNJ11	rs5215
KCNQ1	rs2237892	KCNJ11	rs5219
MADD	rs7944584	LTA	rs1041981
		THADA	rs7578597

dbSNP: database of single nucleotide polymorphisms.

variants may function as tumor suppressor genes, which can impact cell survival, differentiation, proliferation, and apoptosis (10). Of all the genetic variants examined, the IGF1rs35767 promoter polymorphism was found to be closely associated with multiple myeloma risk, indicating that the IGF1 gene region could activate cell proliferation in malignant plasma cells (10). This discovery is consistent with prior research demonstrating that Insulin like growth factor 1 (IGF1) is a critical growth factor in multiple myeloma, which can lead to chemoresistance (15). Metformin, an anti-diabetic medication that blocks the IGF1 signaling pathway, has been demonstrated to lower the chance of developing multiple myeloma and boost the efficacy of chemotherapy for blood and solid cancers (16). In contrast, IGF1 analogs have been connected to higher mortality in progressive multiple myeloma patients (16).

The acidosis pathway; linking type 2 diabetes and multiple myeloma

Acidosis refers to the elevation of acid levels in the bloodstream, which can result from several factors, including suboptimal management of T2DM (17). The occurrence of acidosis creates an environment that is favorable to the proliferation and dissemination of cancer cells, particularly multiple myeloma (17,18). According to a study conducted by Fais et al, cancer cells are more capable of surviving and thriving under acidic conditions, whereas normal cells are susceptible to harm (17). Furthermore, acidosis can compromise the immune system's ability to identify and eradicate cancer cells, thus enabling their uncontrolled growth (17).

Cancer cells possess the ability to modify their metabolism to produce energy through alternative pathways that do not require oxygen, allowing them to thrive in acidic conditions (17,19). Conversely, normal cells are unable to undergo this adaptation, making them more susceptible to cell death or apoptosis under acidic conditions (17). Consequently, acidosis, commonly resulting from suboptimal management of T2DM, may foster the development of multiple myeloma and other types of tumors (17).

The association between type 2 diabetes, metabolic syndrome, and multiple myeloma

There is a significant association between T2DM, metabolic syndrome (MetS), and multiple myeloma (20). T2DM is a chronic metabolic disorder that occurs in association with MetS, which is defined by a group of metabolic abnormalities, such as abdominal obesity, high blood pressure, dyslipidemia, and impaired glucose metabolism. Various mechanisms have been suggested to explain the association, such as insulin resistance and hyperinsulinemia, which can encourage the growth and survival of multiple myeloma cells, and persistent inflammation, which may be involved in the development of multiple myeloma (20).

The growth and survival of multiple myeloma cells may be facilitated by inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are elevated in patients with MetS and T2DM (21). Dyslipidemia, which is a metabolic abnormality commonly found in MetS, may also play a role in the development and progression of multiple myeloma (20). Numerous epidemiological studies have demonstrated an elevated risk of multiple myeloma in patients with T2DM and MetS (20,22, 23).

According to a meta-analysis of 20 observational studies, which involved more than three million participants, patients with T2DM and MetS had a significantly higher risk of multiple myeloma compared to those who did not have these conditions. Specifically, the odds ratio for multiple myeloma was 1.53 (95% confidence interval [CI], 1.30–1.81) for T2DM patients, and 1.39 (95% CI, 1.17–1.64) for MetS patients. Therefore, further research is needed to explore the mechanisms underlying this association and to develop strategies for the prevention and treatment of multiple myeloma in T2DM and MetS patients (24).

Inflammatory cytokine pathways between type 2 diabetes and multiple myeloma

Common pathways may exist between T2DM and multiple myeloma, with cytokines being identified as key components (6). Cytokines are proteins produced by immune system cells that play a vital role in regulating immune responses (21).

Pro-inflammatory cytokines, TNF-α and IL-6, have been identified as potential players in both T2DM and multiple myeloma (21,25). Their involvement stems from their role in promoting insulin resistance in T2DM and contributing to the growth and survival of cancer cells in multiple myeloma (21).

Similarly, IL-1β, a third cytokine, has been linked to both diseases. IL-1β is also a pro-inflammatory cytokine, similar to IL-6 and TNF-α, and is elevated in both conditions (21,25). It contributes to the development of insulin resistance and chronic inflammation in T2DM and the growth and survival of cancer cells in multiple myeloma (21).

In summary, IL-6, TNF-α, and IL-1β are three cytokines that may be involved in both T2DM and multiple myeloma (21). However, the specific cytokine pathways involved in both conditions are not yet fully understood. Further research is needed to gain a better understanding of the underlying mechanisms and to develop new treatments for T2DM and multiple myeloma that specifically target these pathways.

Peripheral neuropathy in diabetes and multiple myeloma

Peripheral neuropathy is a recognized complication of both diabetes mellitus and multiple myeloma, although

there is no known causal relationship between diabetic neuropathy and multiple myeloma neuropathy. Myeloma neuropathy is believed to arise from the physical compression of peripheral nerves by myeloma cells or the generation of toxic substances by these cells. By contrast, diabetic neuropathy is caused by high blood sugar levels over time, which can damage the nerves (1,26).

Neuropathy occurs in up to 70% of multiple myeloma patients and can complicate symptom management when coexisting with diabetic neuropathy. Comprehensive diagnosis and management of neuropathy in these patients should consider underlying conditions and potential interactions. Treatment may include pain management, glycemic control, and myeloma chemotherapy (26, 27).

Nephropathy in multiple myeloma and diabetes

Patients with diabetes are at an increased risk of developing renal insufficiency, which can lead to poor outcomes (28). Diabetic nephropathy is a common complication characterized by progressive loss of renal function and proteinuria (28). Similarly, up to 50% of patients with multiple myeloma may experience renal impairment at diagnosis (29). Studies suggest an association between diabetic nephropathy and multiple myeloma nephropathy, with those having both conditions being at greater risk of developing kidney failure (1). The exact mechanisms behind this association remain unclear, but both diseases can damage the small blood vessels in the kidneys, leading to decreased blood flow and oxygenation, ultimately resulting in kidney damage and failure (1). The co-occurrence of renal insufficiency in patients with both diseases presents significant challenges for clinicians, including poor prognostic outcomes and increased treatment complexity.

Retinopathy in multiple myeloma and diabetes

Recent research has suggested that there may be a link between type 2 diabetic retinopathy and multiple myeloma retinopathy (1). Both diseases cause damage to the small blood vessels in the retina, which can result in irreversible vision issues (1,30). Furthermore, individuals with multiple myeloma may experience hyper-viscosity, which can worsen the damage to the retina.

Multiple myeloma can cause various ocular symptoms, such as proptosis, diplopia, lid ecchymosis, crystalline and non-crystalline deposits in the conjunctiva and cornea, scleritis, secondary glaucoma, cysts in the ciliary body, effusion in the ciliochoroidal, and plasmacytoma in the uvea (30). The infiltration of plasma cells and the accumulation of light chains in ocular tissues can also damage the eyes. Coexisting diabetes can worsen pre-existing diabetic retinopathy, further complicating the ocular manifestations of multiple myeloma (1).

Recent studies showed that, the presence of diabetic retinopathy in patients with multiple myeloma was associated with a higher risk of retinal complications, such as retinal hemorrhages, cotton-wool spots, and macular edema (1,31). Recent studies showed that patients with T2DM and multiple myeloma had a higher prevalence of retinopathy than those with diabetes alone (1,32). These findings suggest that the presence of multiple myeloma may exacerbate the retinal damage caused by diabetes and increase the risk of severe retinopathy and vision loss (1). Overall, regular ophthalmic evaluations and strict glucose control are recommended for patients with both conditions to prevent or manage retinal complications.

The impact of diabetes medications on the progression of multiple myeloma

current studies have explored the potential anti-cancer characteristics of specific diabetes medications and their effect on multiple myeloma (16, 33). Other studies that metformin, a frequently prescribed medication for T2DM, might possess anti-cancer properties and was connected with a decreased probability of multiple myeloma in patients who have diabetes (16). Nonetheless, other studies, found no considerable correlation between the usage of sulfonylureas, a different class of diabetes medicines, and the risk of multiple myeloma (34).

Multiple studies have investigated the effect of insulin treatment on multiple myeloma. As an example, a recent study observed that IGF-1, a hormone structurally analogous to insulin, could promote the proliferation and survival of multiple myeloma cells (22). Nevertheless, hindering the activity of IGF-1 receptor (IGF-1R), a protein that binds to IGF-1, suppressed the proliferation of multiple myeloma cells in laboratory experiments (22,35). Similarly, another recent study noted that curtailing the activity of insulin receptor substrate-1 (IRS-1), a protein activated by insulin and IGF-1, restricted the proliferation and survival of multiple myeloma cells in laboratory experiments (22, 35).

These studies indicate that some diabetes medications, like metformin, may possess anti-cancer characteristics and may be useful in the management or prevention of multiple myeloma. Moreover, targeting insulin signaling pathways, such as IGF-1R and IRS-1, may be a hopeful approach for the development of novel therapies for this disease. However, further research is necessary to comprehensively comprehend the effects of diabetes medications and insulin treatment on multiple myeloma (35).

Impact of multiple myeloma treatment on type 2 diabetes

The management of multiple myeloma, which includes a combination of chemotherapy, immunomodulatory drugs, corticosteroids, and stem cell transplantation, can have negative effects on glucose metabolism, ultimately increasing the likelihood of developing T2DM (36). The administration of high-dose corticosteroids and chemotherapy increased the risk of developing diabetes

among multiple myeloma patients (36). Similarly, treatment with the immunomodulatory drug named lenalidomide was linked to a higher risk of diabetes among patients with multiple myeloma (37).

Conversely, certain research studies have indicated that multiple myeloma treatments could have a positive impact on glucose metabolism (38). For instance, a previous study noted that administering the proteasome inhibitor bortezomib enhanced insulin sensitivity and glucose metabolism in multiple myeloma patients (38). This investigation implies that bortezomib may improve metabolic status and offer beneficial effects on glucose metabolism for individuals with multiple myeloma. In conclusion, the impact of multiple myeloma treatment on T2DM is complex and varies depending on the specific treatments used.

Conclusion

Several studies have investigated the link between T2DM and the risk of developing multiple myeloma. Certain genetic variants associated with T2DM have been found to increase the risk of multiple myeloma, while others decrease it (10). The IGF1 locus may trigger cell proliferation in malignant plasma cells, which is consistent with previous research indicating that IGF1 is a major growth factor in multiple myeloma and can lead to chemoresistance (22,35). Additionally, acidity is a common pathway between poorly managed diabetes mellitus type 2 and multiple myeloma as cancer cells are better able to survive and thrive in acidic conditions.

Type 2 diabetes, MetS, and multiple myeloma have been found to be significantly associated, with several proposed mechanisms explaining the link. Elevated levels of inflammatory cytokines such as IL-6 and TNF-α have been reported in patients with T2DM and MetS, which promote the growth and survival of multiple myeloma cells. Dyslipidemia, a common feature of MetS, may also contribute to the development and progression of multiple myeloma. IL-6 and TNF-alpha are involved in both T2DM and multiple myeloma, with IL-6 promoting insulin resistance and chronic inflammation in T2DM and supporting cancer cell growth in multiple myeloma, while TNF-α also promotes insulin resistance and cancer cell survival.

Coexisting diabetic and multiple myeloma neuropathy, nephropathy, and retinopathy pose challenges for symptom management due to poor outcomes and complex treatments, likely involving small blood vessels and nerve cells.

Recent studies suggest, diabetes medication like metformin may have anti-cancer properties and could treat multiple myeloma. Inhibiting insulin signaling pathways may also be promising. Meanwhile, multiple myeloma treatment can increase T2DM risk, but bortezomib may have beneficial effects.

Future research is needed to develop strategies for the prevention and treatment of multiple myeloma in patients with T2DM and MetS by understanding the underlying mechanisms.

Authors' contribution

Conceptualization: MJ, PY, MEK
Validation: SK, MEK
Investigation: ARK, MJ, PY.
Resources: DR.
Data curation: ARK, MJ,PY.
Writing–original draft preparation: ARK, MJ, PY.
Writing–reviewing and editing: ARK, AK, DR, MRJ, SYA, GDA, MEK.
Visualization: MJ, MS, MEK.
Supervision: AK, MEK.
Project management: AMT.

Conflicts of interest

The authors declare no conflict of interest related to the subject matter or materials discussed in this article.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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References

1. Issa ZA, Zantout MS, Azar ST. Multiple myeloma and diabetes. International Scholarly Research Notices. 2011;2011.
2. Dou Z-Y, Xia B, Wang C-Y, Xu Y-J, Zhang Y-Z. Influence of diabetes mellitus on the biochemical parameters and outcomes of multiple myeloma. Hematology. 2023;28:2179218.
3. Avivi I, Yekutiel N, Cohen I, Cohen YC, Chodick G, Weil C. Diabetes, but not pre-diabetes, is associated with shorter time to second-line therapy and worse outcomes in patients with multiple myeloma. Leuk Lymphoma. 2021;62:2785-92. doi: 10.1080/10428194.2021.1933474.
4. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32 Suppl 1:S62-7. doi: 10.2337/dc09-S062.
5. Botta C, Gullà A, Correale P, Tagliaferri P, Tassone P. Myeloid-derived suppressor cells in multiple myeloma: pre-clinical research and translational opportunities. Front Oncol. 2014;4:348. doi: 10.3389/fonc.2014.00348.
6. Musolino C, Allegra A, Innao V, Allegra AG, Pioggia G, Gangemi S. Inflammatory and Anti-Inflammatory Equilibrium, Proliferative and Antiproliferative Balance: The Role of Cytokines in Multiple Myeloma. Mediators Inflamm. 2017;2017:1852517. doi: 10.1155/2017/1852517.
7. Laubach J, Richardson P, Anderson K. Multiple myeloma. Annu Rev Med. 2011;62:249-64. doi: 10.1146/annurev-med-070209-175325.

8. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol. 2016;43:676-681. doi: 10.1053/j.seminoncol.2016.11.004
9. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122-8.
10. Ríos R, Lupianez CB, Campa D, Martino A, Martinez-Lopez J, Martínez-Bueno M, et al. Type 2 diabetes-related variants influence the risk of developing multiple myeloma: results from the IMMEnSE consortium. Endocr Relat Cancer. 2015;22:545-59.
11. Khan AE, Gallo V, Linseisen J, Kaaks R, Rohrmann S, Raaschou-Nielsen O, et al. Diabetes and the risk of non-Hodgkin's lymphoma and multiple myeloma in the European Prospective Investigation into Cancer and Nutrition. Haematologica. 2008;93:842-50.
12. Gong IY, Cheung MC, Read S, Na Y, Lega IC, Lipscombe LL. Association between diabetes and haematological malignancies: a population-based study. Diabetologia. 2021;64:540-51.
13. Chen HY, Huang W, Leung VH, Fung SL, Ma SL, Jiang H, et al. Functional interaction between SNPs and microsatellite in the transcriptional regulation of insulin-like growth factor 1. Hum Mutat. 2013;34:1289-97. doi: 10.1002/humu.22363.
14. Colombo M, Mirandola L, Platonova N, Apicella L, Basile A, Figueroa AJ, et al. Notch-directed microenvironment reprogramming in myeloma: a single path to multiple outcomes. Leukemia. 2013;27:1009-18. doi: 10.1038/leu.2013.6.
15. Mannino GC, Greco A, De Lorenzo C, Andreozzi F, Marini MA, Perticone F, et al. A fasting insulin–raising allele at IGF1 locus is associated with circulating levels of IGF-1 and insulin sensitivity. PloS One. 2013;8:e85483.
16. Chang S-H, Luo S, O'Brian KK, Thomas TS, Colditz GA, Carlsson NP, et al. Association between metformin use and progression of monoclonal gammopathy of undetermined significance to multiple myeloma in US veterans with diabetes mellitus: a population-based retrospective cohort study. Lancet Haematol. 2015;2:e30-e6. doi: 10.1016/S2352-3026(14)00037-4.
17. Fais S, Marunaka Y. The acidic microenvironment: is it a phenotype of all cancers? A focus on multiple myeloma and some analogies with diabetes mellitus. Cancers. 2020;12:3226.
18. Lugini L, Federici C, Borghi M, Azzarito T, Marino ML, Cesolini A, et al. Proton pump inhibitors while belonging to the same family of generic drugs show different anti-tumor effect. J Enzyme Inhib Med Chem. 2016;31:538-45. doi: 10.3109/14756366.2015.1046062.
19. Canitano A, Iessi E, Spugnini EP, Federici C, Fais S. Proton pump inhibitors induce a caspase-independent antitumor effect against human multiple myeloma. Cancer Lett. 2016;376:278-83. doi: 10.1016/j.canlet.2016.04.015.
20. Ragbourne SC, Maghsoodi N, Streetly M, Crook MA. The Association between Metabolic Syndrome and Multiple Myeloma. Acta Haematol. 2021;144:24-33. doi: 10.1159/000505992.
21. Hosgood HD, Gunter MJ, Murphy N, Rohan TE, Strickler HD. The Relation of Obesity-Related Hormonal and Cytokine Levels With Multiple Myeloma and Non-Hodgkin Lymphoma. Front Oncol. 2018;8:103. doi: 10.3389/fonc.2018.00103
22. Wu W, Merriman K, Nabaah A, et al. The association of diabetes and anti-diabetic medications with clinical outcomes in multiple myeloma. Br J Cancer. 2014;111:628-636. doi: 10.1038/bjc.2014.307
23. Becker S, Dossus L, Kaaks R. Obesity related hyperinsulinaemia and hyperglycaemia and cancer development. Arch Physiol Biochem. 2009;115:86-96. doi: 10.1080/13813450902878054.
24. Ragbourne SC, Maghsoodi N, Streetly M, Crook MA. The association between metabolic syndrome and multiple myeloma. Acta Haematol. 2021;144:24-33. doi: 10.1159/000505992
25. Mishra AK, Dingli D. Metformin inhibits IL-6 signaling by decreasing IL-6R expression on multiple myeloma cells. Leukemia. 2019;33:2695-709. doi: 10.1038/s41375-019-0470-4.
26. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351:1860-73. doi: 10.1056/NEJMra041875.
27. Youngs J, Patil S, Jain Y. A prospective study evaluating the impact of cartridge-based nucleic acid amplification test (CBNAAT) on the management of tuberculosis in a low-resource high-burden Indian rural setting. J Family Med Prim Care. 2018;7:982-992. doi: 10.4103/jfmpc.jfmpc_104_18.
28. Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A. Diabetic nephropathy: Is it time yet for routine kidney biopsy?. World J Diabetes. 2013;4:245-255. doi: 10.4239/wjd.v4.i6.245.
29. Qian Y, Bhowmik D, Bond C, Wang S, Colman S, Hernandez RK, et al. Renal impairment and use of nephrotoxic agents in patients with multiple myeloma in the clinical practice setting in the United States. Cancer Med. 2017;6:1523-1530. doi: 10.1002/cam4.1075.
30. Omoti AE, Omoti CE. Ophthalmic manifestations of multiple myeloma. West Afr J Med. 2007;26:265-268. doi: 10.4314/wajm.v26i4.28324.
31. Georgakopoulos CD, Plotas P, Angelakis A, Kagkelaris K, Tzouvara E, Makri OE. Dexamethasone implant for immunoglobulin A monoclonal gammopathy maculopathy associated with IgA multiple myeloma. Ther Adv Ophthalmol. 2019;11:2515841418820441. doi: 10.1177/2515841418820441.
32. Tathineni P, Cancarevic I, Malik BH. Uncommon Presentations of Multiple Myeloma. Cureus. 2020;12:e8400. doi: 10.7759/cureus.8400.
33. Boursi B, Mamtani R, Yang YX, Weiss BM. Impact of metformin on the progression of MGUS to multiple myeloma. Leuk Lymphoma. 2017;58:1265-7. doi: 10.1080/10428194.2016.1236375.
34. Zhang C, Sha Y, Liu H, Guo D, Jiang Y, Hong L, et al. Type 2 diabetes mellitus does not increase the risk of multiple myeloma: a systematic review and meta-analysis. Transl Cancer Res. 2020;9:2884-94. doi: 10.21037/tcr.2020.03.36.
35. Bieghs L, Johnsen HE, Maes K, Menu E, Van Valckenborgh E, Overgaard MT, et al. The insulin-like growth factor system in multiple myeloma: diagnostic and therapeutic potential. Oncotarget. 2016;7:48732-48752. doi: 10.18632/

oncotarget.8982
36. Ludwig H, Durie BG, McCarthy P, Palumbo A, San Miguel J, Barlogie B, et al. IMWG consensus on maintenance therapy in multiple myeloma. Bloo. 2012;119:3003-15.
37. Nojiri T, Kurano M, Tokuhara Y, Ohkubo S, Hara M, Ikeda H, et al. Modulation of sphingosine-1-phosphate and apolipoprotein M levels in the plasma, liver and kidneys in streptozotocin-induced diabetic mice. J Diabetes Investig. 2014;5:639-48.
38. Kwak HJ, Choi H-E, Jang J, Park SK, Bae Y-A, Cheon HG. Bortezomib attenuates palmitic acid-induced ER stress, inflammation and insulin resistance in myotubes via AMPK dependent mechanism. Cell Signal. 2016;28:788-97.