The Association between Metabolic Syndrome and Multiple Myeloma

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Abstract

Multiple myeloma (MM) is a haematological malignancy arising from monoclonal proliferation of plasma cells in the bone marrow, resulting in the presence of paraproteins or M-protein in serum. The involvement of paraproteins produced by malignant plasma cells in the development of hyperlipidaemia and low-HDL cholesterol has been described, as has an association with MM and obesity, hypertension, and type 2 diabetes mellitus, and insulin resistance, that is, features of the metabolic syndrome (MS). There is an association between MS components, inflammatory cytokines, and the development of MM, and some drugs used in the treatment of MS such as statins and metformin may improve outcomes in MM.

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Introduction

Metabolic syndrome (MS) is a cluster of clinical features usually comprising obesity (central adiposity), with hyperglycaemia and insulin resistance, hypertension, and

dyslipidaemia including hypercholesterolaemia, hypertriglyceridaemia, and low HDL cholesterol and may lead to type 2 diabetes mellitus (T2DM) and cardiovascular disease [1]. There is, however, no universal agreement on the definition of MS, with various suggestions proposed, such as that by the American Heart Association, the International Diabetes Federation, and the World Health Organisation (WHO) [1]. What is agreed upon is the fact that MS is becoming more prevalent given the well-known trend in the growth of human obesity and the factors underlying this are increasing worldwide [1, 2].

The aim of this novel review is to explore the association between multiple myeloma (MM) and components of the MS. Together with central obesity, insulin resistance/hyperglycaemia, dyslipidaemia, and hypertension constitute the MS, widely acknowledged to be associated with increased cardiovascular events and more recently cancer incidence [1].

Obesity

Obesity is an essential component of MS and it is a heterogeneous condition associated with a myriad of pathological processes and disease states. Commonly measured according to the body mass index (BMI), whereby the weight in kilograms is divided by the square

of the height in metres, the WHO classifies obesity (BMI) into 3 distinct stages, namely: stage 1 (BMI 30–34.9), stage 2 (BMI 35–39.9), and stage 3 (BMI ≥ 40). Globally, in 2016, over 1.25 billion adults were found to be overweight (BMI 25–29.9), and 650 million were obese [1]. A BMI >25 was associated with increased all-cause mortality in a pulled analysis of 19 prospective studies that included 1.46 million individuals [2].

New adult cancer diagnoses attributable to increased BMI worldwide in 2012 was estimated at 481,000 cases, with the obesity-attributable cancer burden in the UK calculated to be 8.2 and 4.4% among women and men, respectively [3, 4]. A quarter of these cases ($n = 118,000$) were potentially avoidable had populations maintained their recorded mean BMI of 1982 [3]. Moreover, a separate large prospective cohort study of over 900,000 US adults that analysed the relationship between BMI in 1982 and risk of death from cancer over a 16-year mean follow-up period, whilst controlling for other risk factors (RF), demonstrated that individuals with stage 3 obesity had a relative risk (RR) of death from any cancer of 1.52 (males) and 1.62 (females) compared to their normal-weight counterparts [5]. It is therefore understandable that, as the obesity epidemic continues to expand, there is increasing concern over the growing evidence that links this serious disease with many cancers, including MM [2, 5–9].

The second most common haematological malignancy, MM is an incurable cancer characterized by clonal proliferation of malignant plasma cells of B lymphocyte derivation and concomitant superfluous generation of monoclonal paraprotein, [10, 11]. Several studies have identified excess body weight as an RF for MM development and mortality [5–7, 9, 12–18]. A meta-analysis of 19 prospective studies by Wallin and Larsson [7] reported a statistically significant increased incidence of MM in individuals classified as overweight (RR = 1.12) or obese (RR = 1.21) compared to those within the normal-weight category; RR estimates of MM mortality were 1.15 and 1.54 for overweight and obese individuals, respectively [7]. Furthermore, MM risk and mortality were calculated to increase by 12 and 21% for every 5-unit increment in BMI, correspondingly [7]. Similarly, Calle et al. [5] reported a significantly increased risk of MM mortality for individuals with a BMI of 25–29.9 (RR = 1.18; 95% CI 1.01–1.39 [males]; RR = 1.12; 95% CI 0.93–1.34 [females]), a BMI of 30–34.9 (RR = 1.44; 95% CI 1.10–1.89 [males]; RR = 1.47; 95% CI 1.13–1.91 [females]), and a BMI of 35–39.9 (RR = 1.71; 95% CI 0.93–3.14 [males]; RR = 1.44; 95% CI 0.91–2.28 [females]) compared to in-

Table 1. Summary of studies showing an association between obesity and the risk of developing MM

Study	Type of study
Larsson and Wolk [6]	14,280 individual cases plus a cohort analysis
Wallin and Larsson [7]	15 cohort studies (metanalysis)
Renehan et al. [9]	282,137 individuals (systematic review)
Hofmann et al. [13]	Increased BMI and physical inactivity increase the risk of MM
Lauby-Secretan et al. [14]	Expert opinion, review and metanalysis showed that obesity is a risk factor for MM
Lichtman [15]	Obesity is associated with MM (review)
Murphy et al. [16]	1.3 million individuals (prospective study)
Teras et al. [17]	Review of 20 prospective studies BMI increased mortality
Carson et al. [19]	Obesity is associated with MM (review)

dividuals within the normal-weight category. Moreover, a pooled analysis of MM mortality by Teras et al. [17] that included more than 1.5 million participants from 20 prospective cohorts demonstrated an elevated MM mortality in individuals who had a higher early-adult BMI (hazard ratio [HR] = 1.22; 95% CI 1.09–1.35 per 5 kg/m²) and a higher BMI at cohort entry (HR = 1.09; 95% CI 1.03–1.16 per 5 kg/m²).

Evaluation of the joint effect of young adult and baseline BMI revealed that the heaviest females, both in early adulthood (BMI 25+) and at cohort entry (BMI 30+), were at an increased risk of MM mortality compared to individuals with a “normal” BMI at both time points (HR = 1.95, 95% CI 1.33–2.86), although no such significant association was found in men. Indeed, excess body weight throughout adulthood appears to be an important RF for MM development and mortality [13, 17]. In fact, a prospective study by Nagel et al. [12] in 578,000 adults demonstrated, through Cox regression models, that BMI was the most consistent RF for all blood cancers, especially in women, although no association between BMI and MM was found in males or females. The abundance of evidence that associates a raised BMI with MM has led to the recent establishment of obesity as a recognized RF for MM by the International Agency for Research on Cancer [14]. It has been proposed that the population level my-

eloma burden could be reduced when considering obesity as the only modifiable RF [19].

That said, whether obesity effects the progression of monoclonal gammopathy of undetermined significance (MGUS) to MM remains uncertain. A case control study by Thompson et al. [20] that compared 100 MGUS cases that progressed to MM with 100 age-, gender-, and year of diagnosis-matched MGUS cases that did not progress to MM found no significant association between obesity and progression to MM. However, the study lacked information on recognized RF for MGUS progression and it is difficult to ascertain whether there is truly a lack of a relationship between these factors or whether these results were due to study underpowering. See Table 1 for a summary of studies showing an association between obesity and the risk of developing MM.

Diabetes Mellitus

DM, and more specifically T2DM, has been linked to an increased risk of many cancer types [21–26]. A recent retrospective case review of 82 patients at various stages of their MM disease pathway reported that 58.5% of patients had one or more features consistent with MS, including some with T2DM [25]. Nevertheless, the evidence of the relation between hyperglycaemia and MM is conflicting [12, 27–31]. Khan et al. [27] found no association between the rates of self-reported DM and MM in The European Prospective Investigation into Cancer and Nutrition. Conversely, Nagel et al. [12] reported a positive correlation between blood glucose level and the risk of MM and high-grade B-cell lymphoma in men. Additionally, there was a trend toward significantly increased odds of MM in patients with T2DM in a meta-analysis of 10 studies (OR = 1.22; 95% CI 0.98–1.53; $p = 0.08$) [29].

That said, although the authors addressed age, sex, and geographical location, other important confounders such as obesity and anti-diabetic therapy were not accounted for [29]. A prospective study of US adults documented an increased risk of mortality from MM in women who had a postload plasma glucose concentration ≥ 200 mg/dL (HR = 3.06; 95% CI 1.05–8.93) [28]. Likewise, a Taiwanese study of 310 patients that analysed the impact of preexisting T2DM on the prognosis of MM found that diabetic patients have around a 50% greater all-cause mortality than their non-diabetic counterparts (HR = 1.509; 95% CI 1.023–2.225; $p = 0.037$), with a significantly higher rate of advanced stage and renal impairment at diagnosis [30].

Wu et al. [31] conducted a retrospective review of 1,240 MM patients to evaluate the impact of DM and anti-diabetic medications on MM clinical outcomes. T2DM and steroid-induced DM were present in 12.6 and 31.7% of the cohort, respectively. A significantly reduced overall survival (OS) was found in diabetic patients (median: 65.4 months) compared to nondiabetic controls (median: 98.7 months). In multivariate analysis, steroid-induced DM was a significant predictor of poor OS. Interestingly, metformin use was associated with decreased mortality and insulin analogues with increased mortality from progressive MM [31].

However, it is possible that the increased myeloma deaths in those with DM may be due to poorer health and difficulty tolerating anti-myeloma therapy which may include steroids which are diabetogenic. In addition, those on metformin therapy may have had better diabetes control than those on insulin therapy, which may have been a confounder.

Hyperlipidaemia

Hyperlipidaemia is another component of the MS and has been reported in patients with MGUS and MM, particularly the immunoglobulin (Ig)-A subtype [32–35]. Dyslipidaemia can present as an isolated laboratory finding, with lipid abnormalities that include hypercholesterolaemia, hypertriglyceridaemia, or even chylomicron syndrome, or in combination with its clinical manifestations, such as cutaneous xanthomas, hyperviscosity syndrome, or atherosclerosis [34–37]. A review of 53 cases by Misselwitz et al. [34] that compared hyperlipidaemic MM patients to patients with MM and a normal lipid status concluded a higher incidence of IgA paraprotein (53 vs. 21%), skin xanthomas (70%), and hyperviscosity syndrome (26 vs. 2–6%) in the former patient group [33]. There are also several case reports of acquired myeloma-related phenotypical presentation of Frederickson's type III (raised remnant or intermediate-density lipoproteins; IDL) and type V (raised chylomicron and very low-density lipoproteins) hyperlipoproteinaemia available in the literature [38–40]. Dyslipidaemia associated with MM may be relatively refractory to conventional lipid-lowering medications but responsive to successful MM treatment [34, 35, 41].

Paraproteins have been implicated in the development of MM-associated hyperlipidaemia in a myriad of studies [33, 35, 42, 43]. The mechanism through which this occurs is thought to be the binding of paraproteins to serum

lipoproteins, tissue receptors, and lipoprotein lipase, with a resultant reduction in the clearance of lipoproteins [35, 37, 41–49]. Corsini et al. [43] described a patient with MGUS who had evidence of autoantibodies against the low-density lipoprotein (LDL) receptor, and this was paralleled by Nozaki et al. [41], who demonstrated, through Western blot analysis, the binding of IgA to the LDL-binding site of the LDL receptor in a patient with MM and autoimmune hyperlipidaemia. Similarly, another study revealed IgA autoantibodies to lipoprotein lipase in a patient with autoimmune hyperchylomicronaemia [37]. A case report by Taylor et al. [44] of a patient with MM, generalized plane xanthoma, and hyperlipidaemia illustrated, through immunohistochemical studies of cutaneous lesions and bone marrow, the deposition of IgG with LDL-cholesterol and IgG with β -lipoprotein, correspondingly.

A further study by Kilgore et al. [42] demonstrated an in vitro affinity of the Fab fragment of the IgA paraprotein to apolipoproteins B and E in a patient diagnosed with MM. Cortese et al. [45] compared the metabolism of IDL and LDL-cholesterol in 2 males with Frederickson's type III hyperlipoproteinaemia associated with MM [44].

Compared to controls, the fractional catabolic rate of IDL, the conversion of IDL to LDL, and the affinity of LDL to its receptor were impaired in patients with MM, and this was concluded to be due to the formation of Ig-lipoprotein complexes [46–49]. Many of the studies reported here are case reports of hyperlipidaemia and MM and the current literature is sparse regarding larger epidemiological studies, which would be an important area for future research.

However, it has been suggested that myeloma cells are dependent upon exogenous cholesterol for survival and that LDL cholesterol is an important antiapoptotic [50]. Furthermore, there are data that some myeloma cell lines have defects in cholesterol biosynthesis with abnormality of demethylation of lanosterol to C-29 sterol intermediates [51]. It should also be remembered that an artifactually low HDL cholesterol can be caused by paraprotein interference in vitro with certain HDL assays in Waldenström's macroglobulinaemia [52].

Hypertension

Another feature of the MS is hypertension, and this has also been shown to be associated with MM. Chari et al. [53] reported a higher incidence of hypertension in MM patients. This was also confirmed by Patel and Cornell

[54], who also reviewed increased cardiovascular complications in MM, in part related to insulin resistance, DM, and dyslipidaemia in addition to hypertension. However, it is of course also possible that certain therapies used in MM such as steroids and the selective proteasome inhibitor carfilzomib may also evoke hypertension in some patients [55, 56].

The Innate Immune System

The Crook and Pickup hypothesis may also be pertinent in the context of MGUS and MM progression. Herein, a hypersensitive acute phase response occurs as part of a widespread activation of the innate immune system [57]. Numerous stressors, including infection, inflammation, and malignancy, can induce the release of proinflammatory cytokines, mainly tumour necrosis factor (TNF)- α and interleukin (IL)-6. These subsequently stimulate hepatic production of acute phase reactants, such as C-reactive protein, serum amyloid A, and complement, with marked changes in their serum concentration; metabolic pathways are also influenced with consequent insulin resistance and T2DM [21, 57–59]. Adipose tissue is an endocrine organ that has an active influence on metabolic, inflammatory, and endocrine pathways via the secretion of the aforementioned adipokines, in addition to adiponectin, leptin, and resistin [60–62].

Cytokines and Inflammatory Mediators

Carson et al. [19] hypothesized that the proinflammatory cytokine profile produced by obesity may impact on-cogenesis at several points in the pathway of B-cell differentiation, thereby increasing the risk of MM development. IL-6 is a pleiotropic cytokine with effects on numerous target cells through activation of the antiapoptotic Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway [63, 64]. IL-6 is a powerful myeloma cell growth factor – within the bone marrow, IL-6 produced by both stromal or MM cells has been found to promote myeloma cell proliferation and survival [61–65]. IL-6 and its surrogate markers are poor prognostic factors in MM [66].

There is also a widely established positive relationship between BMI, insulin resistance, and chronic hyperinsulinaemia, which sequentially results in a reduction in the plasma concentration of hepatic insulin-like growth factor binding protein-1 and thus increased free bioactive

insulin-like growth factor 1 (IGF-1) [67, 68]. The literature highlights the pertinent role of IGF-1 in the pathogenesis of MM as it functions to stimulate mitogenesis and survival of myeloma cell lines, as well as promoting MM cell secretion of vascular endothelial growth factor, which facilitates angiogenesis [19, 64, 69–73].

Inversely associated with body fat, adiponectin has anti-inflammatory, anti-atherogenic, and anti-diabetic properties [56, 57, 74, 75]. Its reduced expression may be associated with progression from MGUS to MM [58, 76, 77]. Dalamaga et al. [62] found a significantly increased risk of MM with reduced adiponectin and resistin levels by bivariate analysis in a case-control study that compared the levels of serum adiponectin, resistin, and leptin between 73 patients with MM to 73 age- and gender-matched controls. In the same study, no significant difference was found between the concentration of serum leptin in MM patients compared to controls (after adjusting for variables) despite prior evidence suggesting that the level of leptin, which is positively correlated with fat mass, appears to be higher in MM patients and that leptin concentration may reduce following treatment for myeloma [62, 78–83].

Similarly, a prospective study by Hofmann et al. [80] that evaluated the relationship between serum adipokines and development of MM in 174 MM patients and 348 controls within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial noted a significant inverse association between both total and high molecular weight adiponectin and subsequent risk of MM development, even in patients who were diagnosed with MM 8 or more years following blood collection. Fowler et al. [81] found direct *in vivo* evidence of an association between reduced adiponectin levels and progression of MM with the development of an increased tumour burden and osteolytic bone disease in myeloma-bearing adiponectin-deficient mice.

Moreover, an increased adiponectin level was observed to be protective, inducing myeloma cell apoptosis through activation of AMP-activated protein kinase (AMPK) in concordance with the tumour-suppressive effect of AMPK illustrated in other studies and suggesting that adiponectin may be a novel therapeutic target for MM and the related bone disease [81–84]. This data was supported by clinical evidence of decreased serum adiponectin in MGUS patients that later progressed to MM, and analysis of serum monoclonal protein concentration in this cohort demonstrated a significant inverse correlation between adiponectin and paraprotein concentration [81].

Another possible mechanism for these findings is that adiponectin suppresses nuclear factor (NF)- κ B activation and production of IL-6 and TNF- α [85]; therefore its reduction may contribute to bone marrow overproduction of these cytokines [86]. Interestingly male gender, an established RF for MM, is associated with lower adiponectin levels [87]. Weight loss interventions may thus reduce the likelihood of developing MM and merit further research.

The Impact of Lipid-Lowering and Antidiabetic Medication on MM Cell Lines

Statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase, are widely recognized to exert pleiotropic effects in addition to their lipid-lowering properties [21]. There is accumulating evidence to suggest that statin use may reduce both the risk of development of MM and its mortality [88–91]. *In vitro* studies have shown that statins exert apoptosis-induced effects on myeloma cell lines [88, 89]. Furthermore, a retrospective study of 4,957 patients reported a 21% decrease in all-cause mortality, a 24% reduction in MM-associated mortality, and a 31% reduction in myeloma-related skeletal events in patients with MM who received statin therapy [90].

Epstein et al. [91] assessed the relationship between model statin use (≥ 6 cumulative months) and the risk of MM, with examination of multiple latency periods in a case-control study of 2,532 cases and 9,805 controls. They reported a protective effect of statin therapy on risk of MM after adjusting for serum cholesterol level, with the greatest effect seen in patients who had a period of 48 months or more between the commencement of statin use and the diagnosis of MM, in addition to patients aged ≥ 70 years regardless of the latency period. A period of 48–72 months between initiation of the statin and diagnosis was associated with a 20–28% reduction in MM development as compared to nonusers. Recent commencement of statins (< 36 months) was not associated with a reduced MM risk, suggesting that the beneficial effect of statins in protection against MM occurs early on in the carcinogenic process before the disease is biologically established [91].

Both natural and synthetic statins exert a cytotoxic effect on human myeloma tumour cells through activation of the mitochondrial pathway of apoptosis [92]. It has been suggested that mitochondrial disruption by statins leads to the release of cytochrome c from the intermem-

Table 2. Summary of lipid-lowering drugs including metformin in MM and MGUS

Study	Type of study
Becker et al. [18]	Metformin had antitumour activity in myeloma cell lines (review article)
Otsuki et al. [88]	Simvastatin killed myeloma cell lines (experimental cell study)
Dirks and Jones [89]	Statins killed myeloma cell lines (review)
Sanfilippo et al. [90]	In 2,294 users, statins were associated with reduced mortality (21% decrease in MM)
Epstein et al. [91]	2,532 individuals on statins for 48–72 months showed a 20–28% reduced risk of developing MM
Cafforio et al. [92]	Statins activate apoptosis in myeloma cell lines
Rizos and Elisaf [99]	Metformin decreased mortality in MM (review)
Chang et al. [98]	In MGUS 3% of metformin users progressed to MM compared with 5% non-users
Zi et al. [101]	Metformin killed myeloma cell line (experimental cell studies)

brane space and formation of cytoplasmic apoptosome with activation of caspase 9. This subsequently activates effector caspases and triggers a cascade of events with resultant apoptosis [93–95]. They also impair the production of prenylated proteins leading to impaired cellular signalling and the induction of apoptosis with a potential therapeutic use in MM [96, 97].

Anti-diabetic medications may also have an impact on MM risk and progression [30, 94, 98]. A retrospective study evaluated the effect of metformin use on progression of MGUS to MM in 2,003 patients, 23 and 77% of whom were users and nonusers of metformin, respectively. They found that metformin use for 4 or more years was associated with a reduced risk of transformation to MM (HR = 0.47; 95% CI 0.25–0.87), with a reported 3% of metformin users and 5% of nonusers progressing to MM [99]. Metformin may exert anti-carcinogenic activity through its effect on glycaemic control as well as a direct effect on myeloma cells [30].

Metformin is an AMPK activator, an enzyme that is involved in cellular energy homeostasis and cancer metabolism [98, 100]. Furthermore, a recent study by Zi et al. [101] found that metformin inhibits the proliferation

of myeloma cells by stimulating apoptosis and cell cycle arrest in the G0/G1 phase. Western blot analysis demonstrated that this occurred via a mitochondrial pathway with the activation of caspase 3 and other proapoptotic proteins and the significant inactivation of Mcl-1, a survival protein overexpressed in MM cells and associated with a poor prognosis [101]. The authors also reported that metformin inhibits the expression of insulin growth factor-1 receptor (IGF-1R), phosphatidylinositol 3-kinase (PI3K), protein kinase B (PKB/AKT), and the downstream mammalian target of rapamycin (mTOR) and thereby inhibits the proliferation of myeloma cells via this signalling pathway [101]. There was also a synergistic anti-myeloma effect when metformin was combined with dexamethasone but not bortezomib [101]. It would be interesting to evaluate whether metformin use is additionally protective in the non-diabetic population. Metformin also specifically decreased IL-6R expression in myeloma cell lines [102]. See Table 2 for a summary of lipid-lowering drugs including metformin in MM and MGUS.

Conclusion

Substantial improvement has been made in the treatment of MM, with a current median OS about 7–10 years. The literature indicates an association between features of the MS and MM. The exact reason for this is not clear but may involve adipose derived cytokines and proinflammatory mediators that stimulate plasma cell activity and mitogenesis. In particular, adipocyte secretion of the stimulatory and oncogenic IL-6 appears pivotal in the pathogenesis of MM, which in turn may further elevate lipids. IGF-1 also appears significant in the development of MM, whilst metformin, an AMPK activator, appears to inhibit the proliferation of MM cell lines through the IGF-1R/PI3K/AKT/mTOR signalling pathway and acts synergistically with dexamethasone in the treatment of MM. Thus, addressing obesity may be important in MM. Long-term use of the lipid-lowering drugs the statins use may additionally play a protective role in MM development by impacting on early subclinical disease and sensitizing resistant MM cells to apoptosis.

These observations expose potentially exciting therapeutic interventions in the treatment of MGUS and MM. We would also suggest that the lipid profile, blood pressure, BMI, and glycaemic status be monitored in patients with MGUS and MM and an increased awareness of MS in these patients should be had. However, whilst there is evidence for a relationship between MS and MM, apart

from the importance of controlling MS, there are no clinical trials to date that prospectively address the addition of cholesterol-lowering therapy or metformin usage in the treatment of MM. There are some currently ongoing trials; see clinicaltrials.gov [103], including: metformin and nelfinavir in treating patients with relapsed and/or refractory MM and looking at the clinical activity of metformin with high-dose of dexamethasone in relapse MM (METDEXA-MM). Hopefully such studies will prove fruitful and offer better outcomes for MM patients.

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