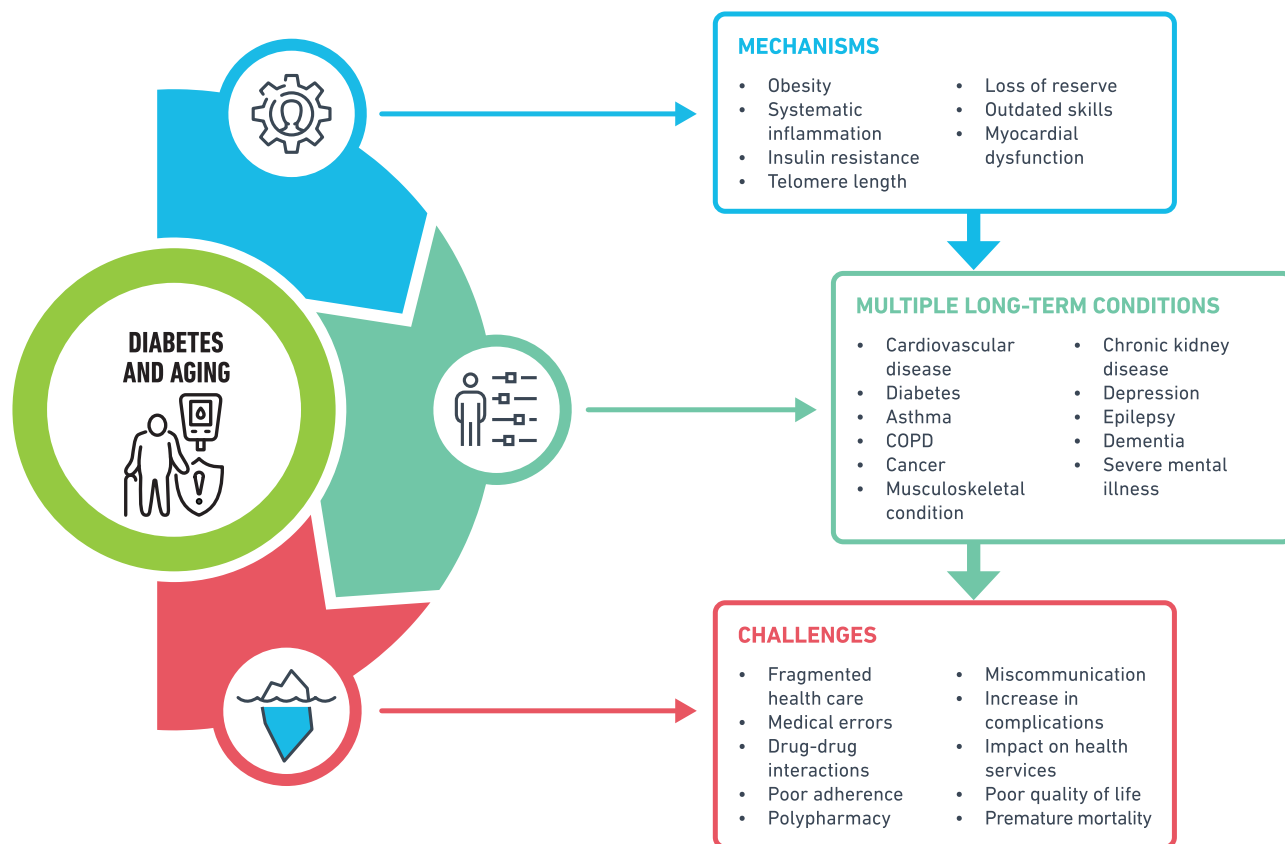


Diabetes and Multiple Long-term Conditions: A Review of Our Current Global Health Challenge

Kamlesh Khunti, Yogini V. Chudasama, Edward W. Gregg, Monika Kamkuemah, Shivani Misra, Jerry Suls, Nikhil S. Venkateshmurthy, and Jonathan Valabhji

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ARTICLE HIGHLIGHTS

- Globally more people with diabetes are living with more than one condition, known as multiple long-term conditions (MLTC) or multimorbidity.
- MLTC is the presence of two or more long-term conditions, with possible combinations of physical, infectious, or mental health conditions.
- MLTC has major implications for the individual such as poor quality of life, worse health outcomes, fragmented care, polypharmacy, poor treatment adherence, mortality, and a significant impact on health care services.
- The key research directions for diabetes and MLTC from a global perspective include system delivery and care coordination, lifestyle interventions, and therapeutic interventions.



Diabetes and Multiple Long-term Conditions: A Review of Our Current Global Health Challenge

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Use of effective treatments and management programs is leading to longer survival of people with diabetes. This, in combination with obesity, is thus contributing to a rise in people living with more than one condition, known as multiple long-term conditions (MLTC or multimorbidity). MLTC is defined as the presence of two or more long-term conditions, with possible combinations of physical, infectious, or mental health conditions, where no one condition is considered as the index. These include a range of conditions such as cardiovascular diseases, cancer, chronic kidney disease, arthritis, depression, dementia, and severe mental health illnesses. MLTC has major implications for the individual such as poor quality of life, worse health outcomes, fragmented care, polypharmacy, poor treatment adherence, mortality, and a significant impact on health care services. MLTC is a challenge, where interventions for prevention and management are lacking a robust evidence base. The key research directions for diabetes and MLTC from a global perspective include system delivery and care coordination, lifestyle interventions and therapeutic interventions.

Diabetes is one of the leading global health challenges of our times. The number of adults living with diabetes globally is 537 million and is predicted to rise to 783 million by 2045 (1). With an increase in the number of effective treatments and management programs, the survival of people with diabetes is therefore contributing to a rise in people living with more than one condition, known as multiple long-term conditions (MLTC) or multimorbidity. This includes a range of conditions such as cardiovascular diseases, chronic kidney disease (CKD), arthritis, depression, and severe mental health illnesses (2). MLTC have major implications for the individual such as fragmented care, polypharmacy, poor quality of life, mortality, and a significant impact on health care services. Clinicians are aware that MLTC are impacting their patients with diabetes but are not able to fully support them, as the current health care system is still designed around the single-disease model (3,4). Thus, clinical decisions are based on multiple guidelines, and clinicians are often faced with many difficulties in balancing the benefits and risks of recommended treatments and consequently give varying advice to patients. For example, younger patients may have complex physical and mental health complications, and older patients may experience a high number of comorbidities with the need for treatment intensification or deintensification and social and quality of life support (5,6).

Previous health reports and reviews to date have highlighted the need to prioritize MLTC (2,7), where the presence of diabetes is associated with a higher likelihood of other long-term conditions being present (8,9). In this review, therefore, we aim to provide a summary of the epidemiology of MLTC in diabetes, challenges for the

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patient and service delivery, and the current interventions for prevention and management. Furthermore, key research directions for diabetes and MLTC are provided.

EPIDEMIOLOGY OF MLTC IN DIABETES

Definition of MLTC

MLTC is defined as the presence of two or more long-term conditions, with possible combinations of physical, infectious, or mental health conditions, where no one condition is considered as the index (10). The term multimorbidity has previously been used; however, following a patient and stakeholder consultation, the preferential description is now MLTC (11). MLTC measures are highly heterogeneous, either based on simple counts of chronic conditions or based on indices to assess the burden by using weights on the range of conditions, duration, severity, and resource utilization such as the Charlson

Comorbidity Index or the Elixhauser Comorbidity Index (12,13). However, data on such indices are often limited (14). In a recent systematic review of 566 studies, investigators reported that the number of conditions measured in MLTC studies ranged from 2 to 285 conditions, median 17, in most cases including a cardiovascular condition (97.6%), metabolic and endocrine condition (97.3%), respiratory condition (93.4%), musculoskeletal condition (87.6%), and mental health condition (78.5%) (15).

Due to the limitations of inconsistent definitions and approaches to measuring MLTC (15), a recent Delphi consensus study included a panel of international experts who identified a definition of MLTC following a criteria relating to the impact of the condition (16). The consensus was reached for defining MLTC as two or more long-term conditions with a duration of ≥ 6 months, with a selected 24 conditions including diabetes to be always included in

the MLTC measure and 35 to usually be included (Table 1). In future studies in MLTC investigators should use this definition by the Delphi study to help facilitate consistency and comparison of studies and to build on the evidence of MLTC research.

Rising Prevalence of MLTC

The prevalence of MLTC to date is highly dependent on the population setting, social determinants such as age-groups and deprivation, health care access and diagnosis, and the number and types of conditions that have been included in the definitions of MLTC. Changes in prevalence may be further influenced by the coding of conditions or the source of data such as primary care, hospitalization, pharmacy, or laboratory. For this reason, it has been difficult to understand the full scale and burden of MLTC (7). Studies usually in the general population report a prevalence between 20 and 30%, and between 55 and 98% in older adults (17,18). Regardless

Table 1—Conditions with consensus to always or usually be included in the MLTC measure, based on Delphi survey (16)

Body system (based on ICD-10 chapters)	Always include, <i>N</i> = 24	Usually include (unless there is a good reason not to in a particular context), <i>N</i> = 35*
Cardiovascular disease	Stroke, coronary artery disease, heart failure, peripheral artery disease	Heart valve disorders, arrhythmia, venous thromboembolic disease, aneurysm, hypertension (treated and untreated)
Metabolic and endocrine disease	Diabetes, Addison disease, cystic fibrosis	Thyroid disorders
Respiratory disease	Chronic obstructive pulmonary disease, asthma	Bronchiectasis
Neurological disease	Parkinson disease, epilepsy, multiple sclerosis, paralysis	Transient ischemic attack, peripheral neuropathy, chronic primary pain
Cancer	Solid organ cancers, hematological cancers, metastatic cancers	Melanoma, benign cerebral tumors that can cause disability
Mental and behavioral disorder	Dementia, schizophrenia	Depression, anxiety, bipolar disorder, drug or alcohol misuse, eating disorder, autism, Posttraumatic stress disorder
Musculoskeletal disease	Connective tissue disease	Osteoarthritis, long-term musculoskeletal problems due to injury, osteoporosis, gout
Digestive disease	Chronic liver disease, inflammatory bowel disease	Chronic pancreatic disease, peptic ulcer
Urogenital disorder	CKD, end-stage kidney disease	Endometriosis, chronic urinary tract infection
Hematological disorder		Anemia (including pernicious anemia, sickle cell anemia)
Eye disease		Vision impairment that cannot be corrected
Ear disease		Hearing impairment that cannot be corrected, Meniere disease
Infectious disease	HIV/AIDS	Chronic Lyme disease, TB, post-acute COVID-19
Congenital disease		Congenital disease and chromosomal abnormalities

*Untreated and treated hypertension were combined. Both sets of panelists agreed to include conditions that require surveillance (including cancers), and thus “cancers that require surveillance” was not stated separately in the list.

of the variability in MLTC prevalence, with the aging population there has been an overall steady rise in MLTC over the years (19) and an increase in targeting MLTC epidemiological studies at younger age-groups and socioeconomically deprived populations and in low- to-middle-income countries (LMIC) (7). Patterns of MLTC have indicated a major increase particularly in cardiometabolic conditions; a cluster analysis study with use of UK Biobank data showed that diabetes was at the center of the disease cluster for MLTC and directly or indirectly related to several other chronic conditions (8,20).

Diabetes-Related MLTC

The classical complications resulting from diabetes are acute metabolic, microvascular, and cardiovascular. Therefore, the development of hyperglycemic states such as diabetic ketoacidosis, and the development of eye disease, kidney disease, foot disease, coronary heart disease, cerebrovascular disease, and peripheral vascular disease in people with diabetes, has long been characterized clinically as “the complications of diabetes.” However, more recently it has been appreciated that many other long-term conditions co-occur in people with diabetes, including conditions that arise by chance and conditions that are associated with diabetes but not traditionally identified as cardinal complications. The presence or absence of the classical complications of diabetes in those with MLTC can allow further categorization of MLTC into concordant and discordant MLTC, respectively, in people with diabetes, where concordant MLTC refers only to the classical complications of diabetes outlined above and discordant MLTC refers to all other long-term conditions.

Examples of conditions associated with diabetes but not traditionally identified as cardinal complications include mental health conditions such as schizophrenia (21), infective diseases such as tuberculosis (TB) and coronavirus disease 2019 (COVID-19) (22), and other physical long-term conditions such as many common cancers, fatty liver disease, obstructive sleep apnoea, dementia, and osteoarthritis of knee and hip. A study of 4,545 primary care patients with type 2 diabetes in Finland showed that 93% of people with type 2 diabetes had MLTC, 21% had a concordant disease, 8% had a discordant disease, and 64% had both concordant and

discordant diseases (23). The concordant diseases included cardiometabolic diseases such as obesity and CKD and discordant diseases included cancer, musculoskeletal disease, respiratory disease, prostatic disease, hypothyroid, dementia or Alzheimer disease, depression, and sleep disorder (23).

Those with long duration of diabetes have a higher MLTC burden mainly characterized by complications such as cardiovascular disease and end-stage renal disease (24). From one U.K. study investigators reported a 33.3% prevalence of one or more comorbid conditions among subjects with type 2 diabetes for the least deprived population and 32.7% for the most deprived (25). In this study hypertension was the most common condition with type 2 diabetes, with the second most prevalent condition in women being depression and for men being coronary heart disease (25). Findings from a U.S. study showed that African American individuals had a higher cardiovascular risk among people with type 2 diabetes compared with White populations, particularly in early-onset type 2 diabetes, with the prevalence of cardiometabolic disease, depression, and diabetes increasing over the past two decades in both African American and White populations (26).

In one recent large study investigators reported an MLTC prevalence of 77% among subjects with type 2 diabetes (27). In this study there was a twofold higher likelihood of schizophrenia, chronic heart failure, hypertension, peripheral vascular disease, and myocardial infarction among those with type 2 diabetes in comparison with those without type 2 diabetes (27). In a U.S. cohort study of 892,233 veterans with diabetes, 52% of subjects had two or more comorbidities, where the odds of having three or more comorbidities were fourfold higher for those age ≥ 75 years and older in comparison with those age < 50 years (28).

Role of Obesity in Diabetes and MLTC

Obesity is increasing in prevalence and is one of the key drivers for the development of diabetes and MLTC. In a recent study where investigators used data from Finland and the U.K. with a 12-year follow-up, obesity was associated with 21 nonoverlapping cardiometabolic, digestive, respiratory, neurological, musculoskeletal, and infectious disease conditions, with obesity being associated with a near 3-fold higher risk for developing at least one obesity-related

disease, 5-fold higher risk for developing two diseases, and 12-fold higher risk for developing complex MLTC. The highest risk associated with obesity is the development of cardiometabolic multimorbidities (type 2 diabetes, coronary heart disease, and stroke) (29). During a mean follow-up of 10.7 years, investigators for one study found that in comparisons with individuals of healthy weight, risk of developing cardiometabolic MLTC in overweight individuals was twice as high (odds ratio [OR] 2.0, 95% CI 1.7–2.4), almost five times higher for individuals with class one obesity (4.5, 3.5–5.8), and almost 15 times higher for individuals with class 2 or class 3 obesity (14.5, 10.1–21.0) (29). The study showed that diabetes-related MLTC was more closely associated with BMI followed by vascular disease (29).

The exact pathways linking MLTC with obesity is unclear but may be related to dyslipidemia and systemic and vascular inflammation, insulin resistance, loss of reserves or frailty, increased thrombogenic factors, and general old age (30,31). Further understanding of causal mechanisms is required, for example, Mendelian randomization studies regarding the central role of obesity in pathogenesis of MLTC (32).

Communicable Diseases and Their Relationship With Diabetes

With the current epidemiological transition and rapid urbanization occurring in LMIC, LMIC are experiencing simultaneous epidemics of both communicable and noncommunicable diseases. We shed light on the complex interplay between key communicable diseases and MLTC.

Diabetes, MLTC, and HIV

People living with HIV (PLHIV) are at increased risk of developing several metabolic diseases, including diabetes (33). Diabetes prevalence ranges from 1.3 to 18% in PLHIV in LMIC (34). These results are consistent with PLHIV in North America and Europe, where differences have been noted in cardiometabolic traits between HIV-infected and uninfected individuals, which may be further modified by use of antiretroviral therapy (ART) (35). Some documented risk factors for type 2 diabetes in PLHIV include traditional risk factors such as age and overweight/obesity and some that are HIV treatment specific including older-generation protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors, lipodystrophy, and hepatitis C co-infection (36).

Findings from observational studies have suggested that HIV infection itself may be a risk factor for type 2 diabetes (37,38). However, the direction of effect is unclear, especially with the use of PI-based antiretroviral regimens, which have been linked to insulin resistance and impaired glucose metabolism (39). Data from population-based surveys in Uganda and Tanzania have shown a large burden of hypertension and risk factors for diabetes in high-HIV burden settings (40). Similarly, in a South African cohort of patients attending primary care services, 75% of those with hypertension had comorbid diabetes (41), while 12% had HIV and type 2 diabetes comorbidity (41). Moreover, ART may adversely affect glucose metabolism through mitochondrial toxicity resulting in dysglycemia (42). Insulin resistance is caused by the direct or indirect effects of both PIs and nucleoside reverse transcriptase inhibitors on mitochondrial function and by chronic inflammatory changes induced by HIV (43), also known as antiretroviral-associated diabetes (44). However, introducing newer ARTs with less metabolic impact could lower diabetes-ART interaction in the future (45).

Some studies suggest that individuals with HIV-associated diabetes may be at a higher risk of developing metabolic syndrome. Evidence suggests that people living with HIV and diabetes are at increasingly higher risk of metabolic syndrome and dyslipidemia compared with people with diabetes but without HIV (46–48). Managing HIV infection and diabetes, as well as addressing other traditional risk factors, can help reduce the risk of developing metabolic syndrome. Regular monitoring, adherence to ART, lifestyle modifications, and appropriate medical management of both HIV and diabetes are crucial for minimizing the risk and complications.

Diabetes, MLTC, and TB. Active TB increases the risk of developing diabetes, as diabetes has also been associated with a threefold increased risk of TB (49). TB/diabetes comorbidity leads to worse health outcomes and prognosis for both conditions (50). Diabetes is associated with a twofold risk of death during TB treatment, a fourfold risk of TB relapse after treatment completion, and a twofold risk of multidrug-resistant TB (51,52). In 2019, it was estimated that >15% of people with TB had comorbid diabetes globally, compared with 9.3% among the general adult population (53). In high-TB

burden LMIC, it is important to have coordinated care and follow-up for both conditions.

Dual and Interacting Epidemics in Rapidly Urbanizing Spaces

Some LMIC such as Africa are currently undergoing an epidemiological transition with changes in disease patterns accompanied by changes in population composition and age distribution (54). The syndemic rise in obesity levels, hypertension, and young-onset diabetes in countries undergoing an epidemiological transition, with co-occurring infectious diseases and non-communicable diseases, raises concerns around a perpetuated cycle of diabetes in high-HIV/TB burden LMIC (55,56). Settings where TB and HIV are endemic require routine monitoring and screening because there may be an undiagnosed burden of type 2 diabetes in the youth with added complexity, as HbA_{1c} has been shown to be less reliable for diagnosis (57).

Diabetes, MLTC, and COVID-19

The World Health Organization declared COVID-19 as a pandemic on 11 March 2020 (58). During the early stages, findings from a modeling study based on the Global Burden of Diseases, Injuries, and Risk Factors Study data suggested that the population at the greatest risk for severe COVID-19 was people with diabetes, cardiovascular disease, CKD, or MLTC (59). Diabetes was reported as one of the most common comorbidities in patients diagnosed with COVID-19, with the prevalence of diabetes ranging from 5.3% to 20.7% (60). Diabetes was associated with a higher risk of death and/or invasive mechanical ventilation at 7 days (hazard ratio 1.42, 95% CI 1.17–1.72) and 28 days (1.30, 1.09–1.55) post-hospitalization in comparisons with those without diabetes irrespective of age and other comorbid conditions (61). Preliminary evidence suggests that people with COVID-19 may be at increased risk of developing type 2 diabetes (incidence rate ratio 1.28, 95% CI 1.05–1.57) in comparison with those with acute respiratory tract infection (62). The crude mortality due to COVID-19 among patients with MLTC was 50% more compared with those without MLTC (OR 1.48, 95% CI 1.26–1.75) (63). Although the most common combination of conditions was stroke and hypertension among patients with severe COVID-19 infection (hospitalization or death) (79%), those with combination of diabetes and CKD has the

highest risk (OR 4.93, 3.36–7.22) of severe COVID-19 infection (64).

MLTC in Special Diabetes Groups

A major challenge of MLTC exists for individuals with diabetes at an earlier age, as they are living with a wide array of conditions for a longer duration.

Early-Onset Type 2 Diabetes

Early-onset type 2 diabetes (diagnosis before 40 years of age) is associated with significant adverse outcomes when compared with a diagnosis later in life (65). The early-onset presentation is concerning from the perspective of MLTC because 1) there is a greater lifetime exposure to hyperglycemia, increasing the risk of diabetes-related morbidity; 2) the phenotype is strongly associated with obesity (66), though not always (67), and appears to have aggressive cardiovascular risk at presentation (26,68), meaning the progression to MLTC may be accelerated in comparison with diagnosis later in life; and 3) the presence of MLTC in people of working age is likely to have a significant economic and societal burden in comparison with the traditional demography.

Taken together, those with early-onset type 2 diabetes should be regarded as the multimorbid population of the future, yet there is very little evidence and, consequently, guidance on best management approaches for prevention and treatment of MLTC and development of services to support affected individuals. These knowledge gaps are important to address, as early-onset type 2 diabetes cases are rising (69).

Several studies have now shown the presence of complications at diagnosis and faster progression to complications in those with early-onset type 2 diabetes. In the landmark Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study of youth with type 2 diabetes (aged <20 years at diagnosis) investigators published 10-year follow-up data on 572 participants; at baseline 19.2% had evidence of hypertension, 20.8% dyslipidemia, and 9.0% presence of a microvascular complication (70). By the end of follow-up, 46.8% of participants had hypertension, 44.4% had dyslipidemia, and 80.1% had one more microvascular complication. With adjustment for sex, race, age, and diabetes duration, the OR for the development of multiple microvascular

complications was highest for the presence of hypertension, 3.18 (95% CI 2.35–4.3), or dyslipidemia, 2.77 (2.05–3.72), and both were higher than the OR for every 1% increase in HbA_{1c}, 1.80 (1.65–1.95). In another study of electronic medical records in the U.S. investigators examined the prevalence of cardiovascular MLTC and depression among individuals with type 2 diabetes diagnosed at ages 18–39 years. At the time of diagnosis, 11% of Black American and non-Hispanic White individuals already had evidence of MLTC, including two or more of the following: myocardial infarction, stroke, heart failure, peripheral vascular disease, CKD, cancer, depression, hypertension, and dyslipidemia (26).

MLTC in early-onset type 2 diabetes may not only be restricted to traditional cardiometabolic comorbidities; results of a recent prospective study of 18,290 incident type 2 diabetes cases developing during follow-up over 38 years demonstrated an association between type 2 diabetes (diagnosed before age 40 years) and risk of cancer, with higher hazard ratio for risk of early cancer diagnosis (1.47, 95% CI 1.06–2.04), diabetes-related cancer (2.11, 1.38–3.23), and obesity-related cancer (1.75, 1.08–2.82), but this was restricted to people with high BMI at age 18 years (71).

Type 1 Diabetes

Type 1 diabetes is an autoimmune condition that does not share traditional cardiometabolic risk factors with many of the comorbidities that predominate in those with MLTC who have type 2 diabetes. Type 1 diabetes does, however, have several facets that predispose to the development of MLTC. First, like early-onset type 2 diabetes, lifetime exposure to chronic hyperglycemia and risks from hypoglycemia increases risk of cardiovascular morbidity from microvascular complications including kidney failure. Second, people with type 1 diabetes carry a higher risk of other autoimmune conditions reflecting underlying genetic predisposition to autoimmunity, and third, it is recognized that there is a significant psychological burden in people with type 1 diabetes that can cause diabetes distress, burnout, depression, and anxiety.

Type 1 diabetes carries a significant risk of cardiovascular disease and mortality that is in excess of the predicted burden from traditional risk factors (72). This risk may be conferred by the long duration of

diabetes; for example, in a Swedish registry study, diagnosis of type 1 diabetes before the age of 10 years was associated with a 30-fold increased risk of cardiovascular disease; women in particular had a 90-fold increased risk of myocardial infarction (72). However, there is evidence of undertreatment of cardiovascular risk in people with type 1 diabetes (73), and the role of cardiac-directed autoimmunity as a proinflammatory state may play a role (74).

The earlier onset of type 1 diabetes results in long-duration type 1 diabetes by early to mid-adulthood. This means people with early-onset type 1 diabetes may be affected by MLTC by their third or fourth decade of life. In a German study with examination of the cross-sectional prevalence of MLTC in 6,967 adult outpatients with type 1 diabetes, investigators demonstrated MLTC in 63.7% of patients. The most common conditions were depression (10.4%), stress reactions (11.7%), hypertension (10.8%), back pain (14.5%), and dyslipidemia (12.1%) (75).

Despite the high risk, systematic studies assessing the breadth of MLTC in people with type 1 diabetes are lacking. However, the clustering of other autoimmune diseases in people with type 1 diabetes has been studied more comprehensively. Of 25,759 individuals studied in the type 1 diabetes network study, 28% had one or more additional autoimmune conditions (76). Factors associated with two or more autoimmune conditions (including type 1 diabetes) included female sex, older current age (and longer duration), earlier age at diagnosis, and White ethnicity. Results of another study of individuals with type 1 diabetes in a U.S. insurance database of 179,248 showed that 27% (95% CI 26.8–27.2%) had at least one concurrent autoimmune disease, hypothyroidism, rheumatoid arthritis, and celiac disease being the most common. In the same study the presence of additional autoimmune diseases was independently associated with increased risk of end-stage renal disease, stroke, and myocardial infarction and these observations were amplified in women.

The current evidence on the epidemiology of MLTC in diabetes has shown MLTC to be a major global health challenge; therefore, understanding the implications for the patient and service delivery is key.

CHALLENGES FOR THE PATIENT AND SERVICE DELIVERY

MLTC is associated with poor quality of life, worst health outcomes, and mortality as well as an impact on health care services (7). Fragmented care is one of the key challenges, where patients are seen by several different health care professionals, for each of their conditions. This can be burdensome for the individual in terms of attending multiple appointments at various locations with limited time for the consultation and may create miscommunication and result in inconsistent health care messages (20). Moreover, polypharmacy, defined as the simultaneous use of five or more chronic medications, can have adverse implications due to the drug-drug or drug-disease interactions; for example, metformin and impaired kidney function are well-known for drug-disease interaction (77). Additionally, multiple drugs can lead to potential side effects, medical errors, and poor adherence.

There is a great impact on health care service delivery, diabetes is associated with a higher number of comorbidities and risk of cardiovascular events, requiring frequent general practitioner and specialist consultations, and hospital appointments or admissions. Results from a recent study from England of 120,499 adults with newly diagnosed type 2 diabetes between 2000 and 2018 showed that the mean annual inflation-adjusted cost for face-to-face consultations was £412.70 per patient without comorbidities, £516.80 for one comorbidity, £620.75 for two comorbidities, and £778.83 for three or more comorbidities (78). In another Spanish study of nearly half a million people with type 2 diabetes, investigators reported that 70% had MLTC and also reported an increase in cost related to MLTC, where the highest was for insulin (average cost €153) or oral antidiabetes agents (€306) and combinations, for people with diabetes who also had cardiovascular disease and neoplasm (79).

CURRENT INTERVENTIONS FOR PREVENTION AND MANAGEMENT

Recognition of the range of MLTC associated with diabetes has motivated researchers and clinicians to develop and implement several management approaches, which can be framed as 1) system delivery/care coordination, 2) lifestyle interventions, and 3) therapeutic interventions (Fig. 1).

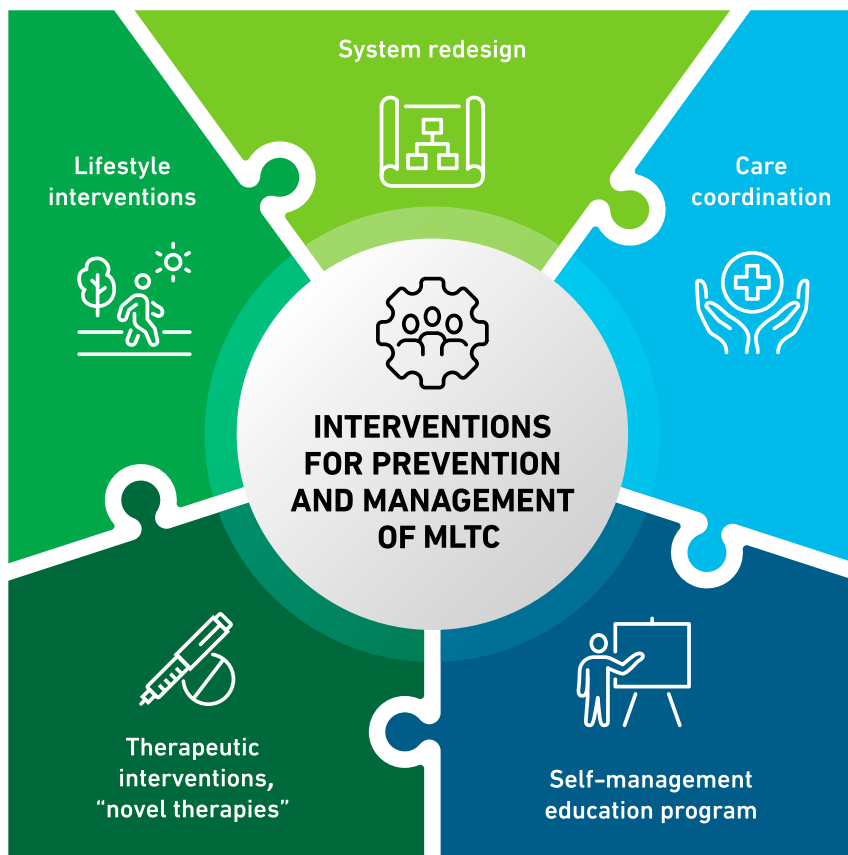


Figure 1—Interventions for prevention and management of diabetes and MLTC.

System Delivery and Care Coordination

There has been a limited number of interventions that have targeted the coordination of care and self-management support for MLTC (not diabetes specific) since 2011, when the first randomized controlled trial was published (80). One of the largest studies to date involved a three-dimensional review of the patient's health, including information on depression and medications, during an appointment with a nurse and a records-based medication review by a pharmacist (81). A responsible physician then received this information and discussed a collaborative treatment plan with the patient and provided a printed plan of agreed goals. The three-dimensional intervention versus usual care was tested in a cluster randomized trial in England and Scotland with a 15-month follow-up with health-related quality of life as the primary outcome. Although no differences were found in health-related quality of life, patients perceived improvements in the quality of their care (81). In an updated Cochrane review of trials testing the effects of system intervention

versus usual care investigators similarly found that patient perceptions of health care may improve, but the evidence was considered limited because of the variation in study participants and interventions (82).

Two trials in primary care networks including people with type 2 diabetes and MLTC involved in-home visits, care coordination by nurses or specially trained medical assistants, and periodic team case conferencing to enhance self-care (83,84). Comparisons with usual-care control subjects showed no significant differences in patient-reported physical and mental functioning or health-related quality of life. The variation in comorbidities and participants may be responsible, but thus far system delivery/care coordination has had only modest success.

Lifestyle Interventions

There is good evidence from randomized controlled trials that behavioral interventions to support people at high risk of developing type 2 diabetes to lose weight, adopt a healthy diet, and increase physical activity can significantly decrease the

incidence of type 2 diabetes (85,86). Translation of this evidence to diabetes prevention programs delivered at scale in the real world and across national footprints has now demonstrated similar benefit (87,88). Evidence that lifestyle interventions directly affect the development of MLTC per se, rather than specific disease progression, is also now emerging. There is evidence for intensive lifestyle interventions preventing MLTC in both those with type 2 diabetes and those with prediabetes. The Look AHEAD (Action for Health in Diabetes) trial included middle-aged overweight or obese individuals with type 2 diabetes and achieved its primary goal to produce a 7% weight loss and cardiovascular fitness. Although no differences were found for cardiovascular outcomes, the intensive lifestyle intervention slowed the rate of increase in MLTC with time (89). In the 30-year follow-up of the Da Qing Diabetes Prevention Outcome Study, those with impaired glucose tolerance who underwent a lifestyle intervention still had lower type 2 diabetes incidence as well as reduced incidence of cardiovascular events, microvascular complications, and cardiovascular and all-cause mortality (90).

Lifestyle interventions tend to offer more positive evidence than system delivery. The choice of primary end point for interventional studies aiming to improve outcomes in those with type 2 diabetes and MLTC is important, but international agreement has been lacking. Although a recent Delphi consensus study was focused on which disease states to include in the MLTC definition (16), agreement on which end points to apply for interventional studies for MLTC is lacking, and choice of an end point is to some extent likely to be disease combination specific. Health-related quality of life has received somewhat more study, which is consistent with the promotion of patient-centered care, but health-related quality of life may be insufficiently sensitive to differentiate what is or is not a contributory intervention.

Therapeutic Interventions

Therapeutic interventions for risk factor management in people with diabetes can involve multiple different drugs and classes of drugs to be taken daily—usually including several glucose- and blood pressure-lowering agents as well as a statin. With concurrent diabetes complications and/or more diverse long-term conditions, the

number of drugs to be taken will be even greater. The major determinant of progressive MLTC is aging, and many older people are on weight loss trajectories, associated, for example, with cognitive impairment, frailty, or cancer diagnoses. Without deintensification in medications, aging and polypharmacy in those with diabetes and MLTC can therefore be associated with harms due to overtreatment, specifically related to hypoglycemia, postural hypotension, and falls. As a result, clinical guidelines that relate to MLTC often incorporate medicines management protocols with the aim of deintensification of therapy where deemed appropriate (2,91). This has been highlighted as important in those with diabetes where hypoglycemic risk is significant, particularly in people with CKD and dementia treated with sulfonylureas or insulin (92,93), and diabetes overtreatment has been associated with increased mortality (94). However, investigators of a recent systematic review of deprescribing antihyperglycemic medications in older adults with type 2 diabetes found that while deprescribing is likely feasible and safe and benefits may outweigh the harms, the evidence indicated very low certainty (95).

Newer classes of glucose-lowering medications that carry lower risks of hypoglycemia and have multiple beneficial targets of action have therefore been suggested as more attractive in the context of MLTC (30). For example, sodium-glucose cotransporter 2 inhibitors, in addition to lowering glucose, have been shown to reduce cardiovascular mortality, heart failure hospitalizations, and kidney complications (96) and feature prominently now in national and international guidelines (97,98). Similarly, glucagon-like peptide 1 receptor antagonists, in addition to lowering glucose, reduce weight and reduce risk of cardiovascular disease (99), although whether the associated weight loss is advantageous in more elderly cohorts with MLTC, who may already be on weight loss trajectories, is unclear.

The role of metformin in the prevention of MLTC is also currently being indirectly explored: the aim of the Targeting Aging with Metformin (TAME) is to test the hypothesis that human aging can be targeted and a number of age-related outcomes prevented, potentially delaying the aging process to improve human health span by modulating pathways involved in aging (100).

KEY RESEARCH DIRECTIONS

The existing literature to date has demonstrated significant progress in identifying the issues relating to diabetes and MLTC. However, further research is crucial to be able to develop a robust evidence base.

The key research directions for diabetes and MLTC from a global perspective are as follows:

1. Identifying the commonest clusters of MLTC in people with diabetes.
2. Systematic studies of MLTC in diverse populations with early-onset type 2 diabetes are lacking. In particular, a better understanding of the trajectory for the development of MLTC and the clusters that form would be useful to help design studies that can prevent MLTC but also tailor services to these groups.
3. The economic impact of people of working age developing MLTC in type 2 diabetes is also unknown.
4. The epidemiology of the evolution of MLTC in type 1 diabetes requires further study, but the question of how best to prevent and support MLTC in type 1 diabetes is very important.
5. Answers to simple questions are unknown, e.g., optimal age for starting statin therapy, especially in those with early-onset type 1 diabetes who already have long-duration well before the age of 40 years, or whether the presence of other autoimmune diseases should prompt more aggressive risk reduction.
6. Do the risk factors for MLTC differ qualitatively from the risk factors of the constituent conditions of MLTC?
7. Do the interventions that affect MLTC differ from the interventions that are effective in reducing the progression of the constituent conditions of MLTC?
8. In LMIC how can primary health care systems be strengthened to address the growing burden of MLTC?
9. How can existing single disease-focused national programs (e.g., HIV, TB) be integrated with noncommunicable disease programs to provide MLTC care in LMIC?
10. What are the most cost-effective models of care for people with diabetes and MLTC?
11. Evaluation of therapeutic target(s) for prevention and management of MLTC.

12. Evaluation of health delivery models; e.g., remote to virtual (mHealth) technologies might be used to send text messages to inform and prompt patients concerning topics such as medical adherence and increasing physical activity.

CONCLUSION

The main clinical and research directions for diabetes and MLTC from a global perspective will include system delivery and care coordination, lifestyle interventions, and therapeutic interventions. This will require a multidisciplinary approach, including clinical experts, specialists, researchers, and people with MLTC, to develop interventions to improve the lives of people with MLTC and to build future cost-effective health care systems to deliver.

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