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BURDEN OF LIPOHYPERTROPHY AMONG INSULIN DEPENDENT DIABETES MELLITUS PATIENTS IN CHINA: AN ANALYSIS OF OUTCOMES AND IMPACT OF PEN NEEDLE REIMBURSEMENT POLICY

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BURDEN OF LIPOHYPERTROPHY AMONG INSULIN DEPENDENT DIABETES MELLITUS PATIENTS IN CHINA: AN ANALYSIS OF OUTCOMES AND IMPACT OF PEN NEEDLE REIMBURSEMENT POLICY

A DISSERTATION

by

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ABSTRACT

Burden of lipohypertrophy among insulin dependent diabetes mellitus patients in China: An analysis of outcomes and impact of pen needle reimbursement policy

by

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Background

Diabetes is a global epidemic and with an aging population accompanied by rapid urbanization China ranks highest in disease prevalence and associated burden. Independent of diabetes type, insulin is an eventual and costly requirement for disease management. The consequences of insulin administration however are poorly understood. Lipohypertrophy (LH) is one such consequence. It is hypothesized that method of insulin delivery and poor delivery technique are significant risk factors for this condition which is believed to alter insulin pharmacodynamics. Subsequently, insulin pen needles are a critical component of care however access to pen needles varies across China.

Objective

The objective of this study is to characterize the insulin injecting population in China, determine the prevalence of LH and highlight attributable risk factors. This research is also intended to explore the relationship between pen needle reimbursement policy, injection practices, clinical outcomes and direct costs among insulin injecting diabetics in China.

Methods

A cross-sectional examination was conducted among 401 insulin users with Type 1 or Type 2 diabetes treated in outpatient endocrinology units of four large tertiary care hospitals in Nanjing, Chongqing, Beijing and Zhengzhou. Eligible participants were between the ages of 18-80 and taking insulin for a duration of greater than 1 year. Demographics, medical history including HbA1c, healthcare resource utilization (HRU), out-of-pocket costs, insurance and PN reimbursement status were surveyed. LH prevalence was clinically confirmed at the time of examination. Differences between those with and without LH were evaluated by Student's t-test or Wilcoxon rank sum. Unit costs were assigned to insulin and healthcare HRU and compared using descriptive statistics and multivariate regression models.

Results

A total of 403 patients provided informed consent of which 401 completed the clinical module of the survey and 400 completed the HRU section. Half the study population was male (49.9%) with an average age of 59.6 year and BMI of 25.4 kg/m^2. Most patients in this study were diagnosed with Type 2 diabetes (93%) and had diabetes for an average duration of 11.8 years and using insulin for 5.8 years (range 1-29.3 years). Prevalence of LH in this population was established to be 53.1%.

More than half the study population reported at least one diabetes related outpatient (OP) visit (62.7%) and 14.4% of the sample had at least one hospital stay in the past 6 months. The average number of diabetes related OP visits and hospital stays per patient was 2.55 (SD 2.55) and 0.177 (SD 0.516) respectively. The average daily insulin dose was 33.95 (SD 18.41) with patients reporting a range from 6 -118 units per day. Nearly 100% of study participants had some health insurance coverage (98%) and 35.5% had coverage for insulin pen needles.

LH prevalence was observed to be 18.6% higher in those without PN reimbursement (59.3% vs. 40.7%, $p=0.0007$). LH patients also exhibited higher HbA1c (8.2 vs 7.7%), insulin consumption (11U), median PN reuse (12 vs. 7 times per needle, $p<0.0001$), and costs (6-month insulin costs 1591 vs. 1328 RMB, $p=0.0025$; 6-month total HRU 6433 vs. 4432 RMB, $p<0.0001$). Injection site rotation and PN reuse frequency were both identified as risk factors for LH along with BMI and reimbursement. Incorrect injection site rotation had an odds ratio of 8.4 ($p\leq0.001$).

Total cost of excess insulin consumption adjusted for adherence was estimated to be $313 million 2015 USD.

Conclusions

LH widespread complication among the insulin injecting diabetic population in China. LH is associated with higher insulin consumption and worse glycemic control. Insulin users without PN reimbursement may pose a greater economic burden to China compared to those with PN reimbursement. Injection site rotation and reduction in needle reuse may limit the development and impact of this complication. Furthermore, broader coverage for PN may reduce clinical and economic burden on the patient and healthcare system while improving quality of care.

ACKNOWLEDGEMENTS AND DEDICATIONS

"We are a product of those who taught us, who gave us an opportunity, who have given us chances, who've inspired us." – Thomas Keller

I would like to express my deepest appreciation to my dissertation committee for transcending this poignant journey of education, experience and stamina with me. I would like to especially thank Professor William T. Gallo, for being my mentor, recognizing my strengths and giving me the courage to focus on being the best at what I do. Also, to my family who have made innumerable sacrifices to ensure that I not only have opportunity, but the courage to seize it.

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DISCLOSURE STATEMENT FOR CONFLICT OF INTEREST

The author has no conflicts of interest and nothing to disclose.

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SECTION 1: INTRODUCTION

Health care access and chronic disease management

Access to healthcare has long been implicated as a reason for poor utilization of health services. The difference between these two concepts stems from the belief that appropriate access to care implies equity, or the lack of "systematic differences" between patients with or without access, whereas utilization refers to the consumption of services, such as outpatient/inpatient visits or prescriptions filled. Essentially, access encompasses both unmodifiable (e.g. race/ethnicity, age, gender) and modifiable (e.g. income, education level, insurance status, neighborhood/ community factors) elements, which can either facilitate or preclude individuals' utilization of health services. The Institute of Medicine's (IOM) definition of healthcare access—" the timely use of personal health services to achieve the best possible health outcomes"—makes clear that patient utilization and outcomes are inextricably linked to healthcare access[1-3].

The principal objective of a healthcare system is to foster or sustain individual and population health. For individuals who have already developed a noncommunicable (or chronic) disease, studies have reported that the delivery of disease self-management programs and health education have positively affected health and economic outcomes[4]. Yet, other factors may influence the effectiveness of these programs, including demographic attributes, health literacy and insurance and access to care. A systematic review of health literacy and health outcomes demonstrated a strong association between low health literacy and numerous adverse outcomes, including high health resource utilization, fewer screenings, poor adherence to medications and poorer overall health and health outcomes[5]. Health insurance, a key factor in access to care (i.e., insurance is frequently necessary for patients to afford medical care), has moreover been found to be protective among patients with chronic disease, with studies' reporting that insured patients and those who hold additional drug coverage are more likely to have better health outcomes than those who lack such coverage[6,7].

Preventative care is a critical element in the maintenance of well-being, particularly individuals at pronounced risk for chronic disease. The logic is intuitive. In seeking preventative care, patients at risk for chronic conditions will be diagnosed and treated promptly, which establishes the foundation of disease management. Quite the opposite, patients who do not seek preventative healthcare services will be diagnosed much later in the disease process, raising the potential for more acute care and lower likelihood of successful clinical or self-management[2,8]. Late-stage disease activity for unmanaged patients often presents with greater symptom severity and worsened functionality than among patients who are diagnosed and seek treatment at earlier stages of disease. In the cases where financial burden and access to care preclude earlier management, greater outcome severity ensues. In vascular disease, socioeconomic disadvantage has been correlated with greater need for surgical procedures, and may lead to a higher likelihood of limb amputation, which is indicative of end-stage disease[9, 10]. In dyslipidemia, cardiovascular disease, and diabetes, lack of insurance coverage and underutilization of health services have been associated with underuse of services and poorer health outcomes[11-13].

While the scientific literature has established a relationship between access to healthcare and disease severity, the mechanism by which these two domains are linked has yet to be clearly established. One proposed mechanism is that reduced access to care delays disease management, which then leads to greater severity of disease; this translates to worsened outcomes in the long-term, because prescription medications and self-management techniques have a shorter window of time to produce an effect. Another possibility is that health education modifies the relationship between access to care and disease severity. Despite the mechanism, the multiple burdens of suboptimal healthcare access, both direct and indirect, are primarily borne by the patient. When aggregated, access problems are costly depletors of economic value and social value[7].

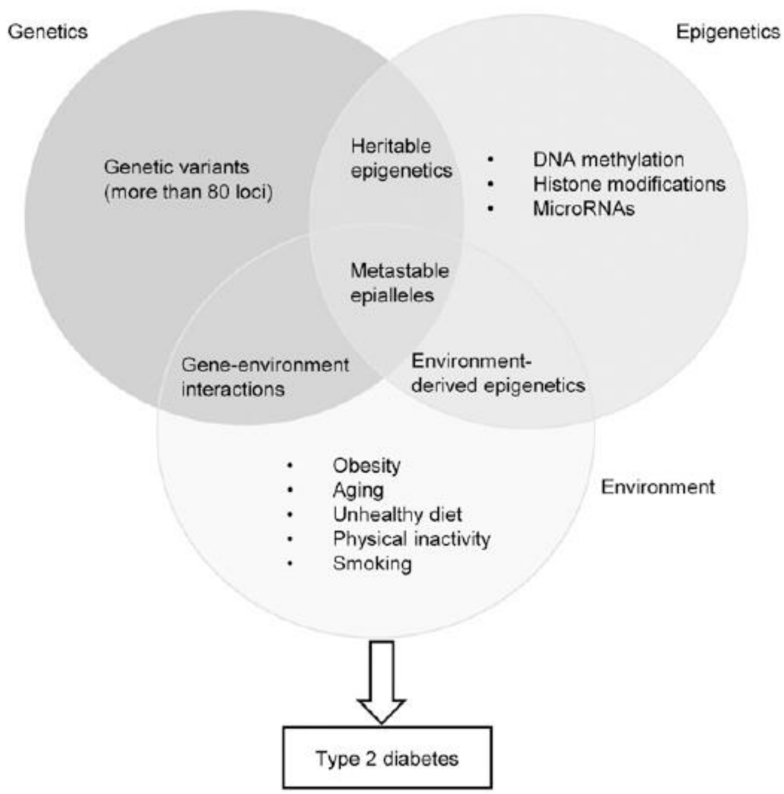
Diabetes

Diabetes is a condition of the pancreas that occurs as a result of poor insulin production or insulin resistance. The insulin hormone produced in the pancreas is the primary transport mechanism for glucose in the blood to be moved to cells where it can be further broken down and utilized. Thus, a diagnostic marker for this disease is the presence of excess glucose in the blood. If elevated glucose levels are left unaddressed, a patient is at risk for serious comorbidities, including cardiovascular disease, kidney damage, nerve damage and eye disease. Secondary to these conditions are amputation and blindness. Although diabetes and the underlying beta cell damage in the pancreas cannot be reversed, effective management of the condition can delay or entirely prevent complications.

There are three main types of diabetes including Type 1, Type 2 and gestational. Type 1 diabetes is believed to be caused by an autoimmune response that ultimately incapacitates insulin-producing beta cell function. This condition most often occurs during childhood or adolescence, and insulin therapy is compulsory for survival. Symptoms may include abnormal thirst, frequent urination, fatigue, hunger, sudden weight loss, bed wetting and blurred vision[14,15].

Type 2 diabetes is the most prevalent type, and accounts for 90% of the disease burden worldwide. Type 2 diabetes is characterized by insulin resistance whereby insulin is still produced (although inadequately), however the body is unable to effectively utilize it, leading to a rise in available blood glucose. Type 2 diabetes has a slow onset, and is most often seen in older adults. Nevertheless, adolescent prevalence of the disease is on the rise, consistent with increases in childhood obesity. Due to the lack of physical symptoms associated with Type 2 diabetes, the number of undiagnosed patients is also believed to be significant. Patients may, moreover, feel less urgency to manage the condition. Delaying treatment, however, results in the same complications as Type 1 diabetes over the longer term. The causes of Type 2 diabetes are not known, however there are strong linkages with a combination of genetic and modifiable risk factors (Figure 1.1)[14,15].

Figure 1.1. Interaction Model for Type 2 Diabetes Risk[16]



Gestational diabetes, also referred to as hyperglycemia in pregnancy, is a condition that most commonly afflicts women during the second or third trimester of pregnancy. In this case, insulin resistance occurs due to the interference of hormones produced by the placenta. Gestational diabetes commonly resolves after childbirth; however, there is an increased risk of developing gestational diabetes during future pregnancies. In addition, approximately 50% of women with gestational diabetes develop Type 2 diabetes within 5-10 years. Gestational diabetes can lead to high blood pressure, larger birth weights, and in some cases, difficult deliveries. The condition is diagnosed using an oral glucose tolerance test[14,15].

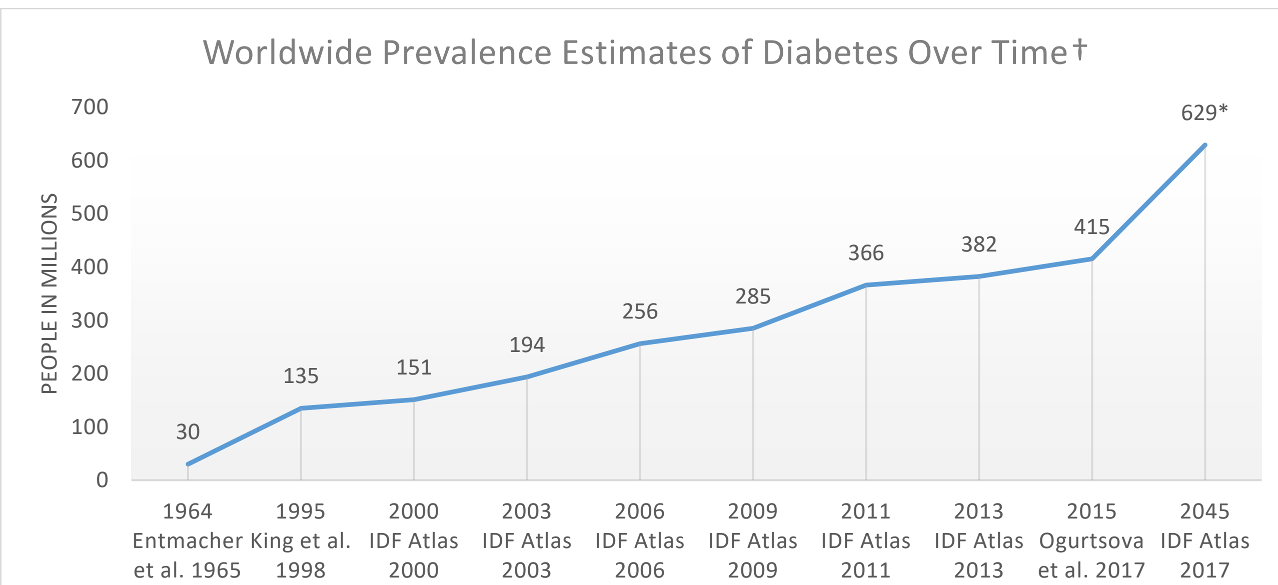
Diabetes Management

The goal of diabetes management is to regulate the body's insulin response in order to optimize glucose utilization and avoid associated complications, such as renal failure, retinopathy, neuropathy or amputation. Proper diabetes management may also reduce the risk of cardiovascular disease in at-risk patients. Lifestyle interventions are normally the first line of defense for individuals with pre- or early onset- diabetes. These interventions may include modifications in diet and physical activity in addition to health education for patients and caregivers. When such interventions are no longer independently adequate, health practitioners turn to pharmacotherapies, specifically oral antidiabetic agents (OAD). The first-line OAD for patients with Type 2 diabetes is metformin, which works to improve the body's response to its own insulin while reducing glucose production in the liver. OADs are not curative, and are intended only to slow the progression of diabetes. When metformin is no longer effective in maintaining glycemic control, second-line agents, such as sulfonylureas, glinides, thiazolidinediones, and dipeptidyl peptidase 4 inhibitors, are typically added for additional control. Eventually, beta cell dysfunction in all diabetic patients reaches a point where insulin or insulin analogs become mandatory for blood glucose management to avoid serious complications of the disease[15,16].

Burden of Total Diabetes

Diabetes is one of the World Health Organization's top 10 noncommunicable diseases and is responsible for 4% of all noncommunicable disease-related deaths[17]. In addition to its critical mortality implications, diabetes has substantial morbidity and economic ramifications, further validating this condition as a serious global public health concern. In 2015, the International Diabetes Federation (IDF) estimated that 415 million people (9.1%) worldwide had diabetes, reflecting nearly a tripling in disease prevalence in a period of two decades (Figure 1.1). The changing demographic and socioeconomic patterns around the world are expected to further increase the number of people who are at risk for diabetes and who eventually develop the disease. As the population ages, and such risk factors as obesity, high cholesterol and hypertension continue to rise at an equally alarming pace, the IDF has conservatively projected the global prevalence of the disease to exceed 640 million individuals by 2040 (Figure 1.2)[18].

Figure 1.2. Prevalence of Diabetes 1965-2040[18-26]



*Projected prevalence
†Trend line not to scale

The prevalence of diabetes is noted to be disproportionate among those living in middle- and high-income countries, and 75% of all people with diabetes were found to be living in low-to-middle income countries. Over half of the global diabetic population is concentrated in South-East Asia and the Western Pacific region, with China and India leading the way with the most number of adults living with diabetes. China and India also spend the least per capita on management of the disease[18,14].

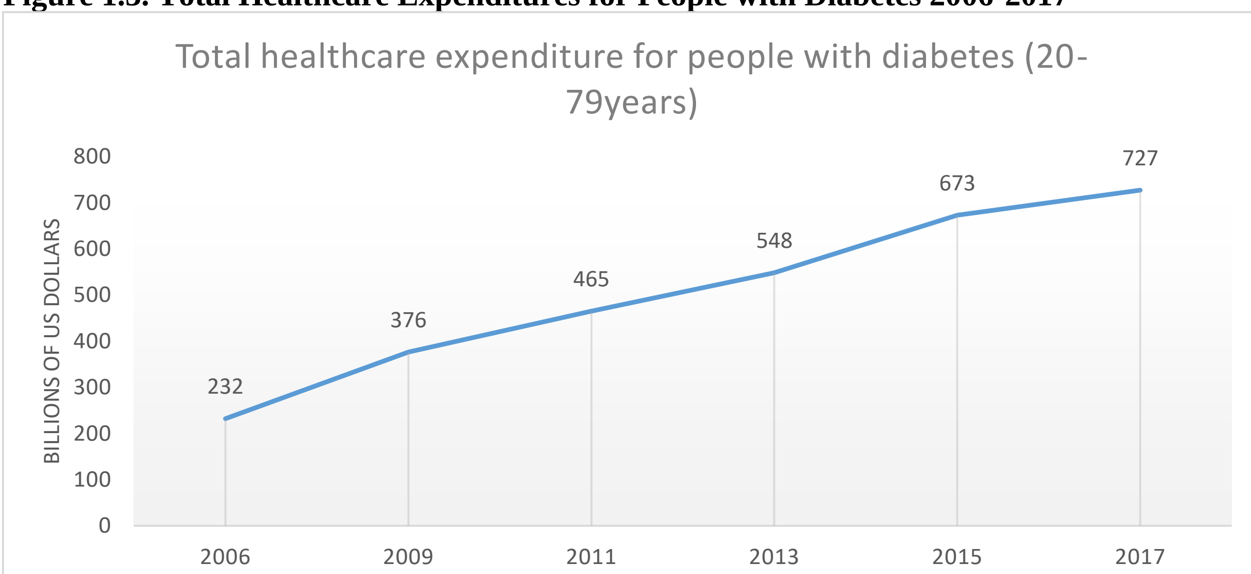
Like many chronic conditions, diabetes prevalence and incidence can be triggered or exacerbated by a variety of influencers. Research has substantiated that the most influential behaviors in the development of Type 2 diabetes are those stimulated by urbanization, whose potential mediating effects include changes in nutrition, decreased physical activity and more sedentary lifestyles. Furthermore, randomized clinical trials from have demonstrated that modification of these behaviors can avoid or delay the onset of Type 2 diabetes[27-29,14].

Once diagnosed, diabetes requires a great deal of clinical management to prevent disease progression and development of commonly associated comorbidities. This management includes regular lab tests, physical examinations focusing on healthy eye and foot care, regular vaccinations, and cholesterol management[30]. There is also evidence to support the efficacy and economic benefits of secondary prevention (e.g., controlling glucose, lipid, and blood pressure levels) and tertiary prevention (e.g., screening and treating early for early diabetes complications). Unfortunately, these scientifically and economically justified prevention programs are not often effectively used in clinical practice, often due to the lack of patient access or inability to drive scale in priority areas[31-33].

Economic Burden of Diabetes

Without proper management of the condition the global population will be subject to deteriorating health while faced with the pressures of increasing healthcare expenditures. Since the International Diabetes Federation started tracking global diabetes-related healthcare expenditures in 2006, there has been a threefold increase in spending (Figure 1.3). In the most recent assessment of healthcare expenditures associated with diabetes, the IDF estimates diabetes to cost in excess of $727 billion USD globally in 2017. When expanding the age groups for this estimate to 18-99 years, this cost jumps to $850 billion. At the country level, the highest expenditures were observed in the US ($348 billion) followed by China ($110 billion). However, China falls off the top 10 list when calculating diabetes expenditure per capita, leaving the US in the number one spot ($11,638/person). Diabetics between the ages of 60-69 pose the largest economic burden, with an expenditure of ($127 billion), followed by those ages 70-79 ($86 billion). This burden is largely due to the nature of the progression of the condition and incidence of diabetes-related comorbidities later in life.

Figure 1.3. Total Healthcare Expenditures for People with Diabetes 2006-2017[14]



When compared to the general population, people with diabetes use a greater amount of healthcare resources, including in- and out-patient services, medications, and long-term care. They have a higher probability of being hospitalized or requiring emergency care, which are contributors to the magnitude of healthcare dollars spent on this population. What is not well summarized in the global literature is the expanse of indirect costs associated with this population. Indirect expenditures may include transportation expenses to seek care, accommodation expenses, social or workplace productivity loss, nutritional expenses or opportunity cost due to premature death or disability[34]. A 2017 report estimated that the inclusion of indirect costs, in addition to those associated with diabetes-related complications such as cardiovascular disease, raised the total cost of diabetes to $1.3 trillion USD[14].

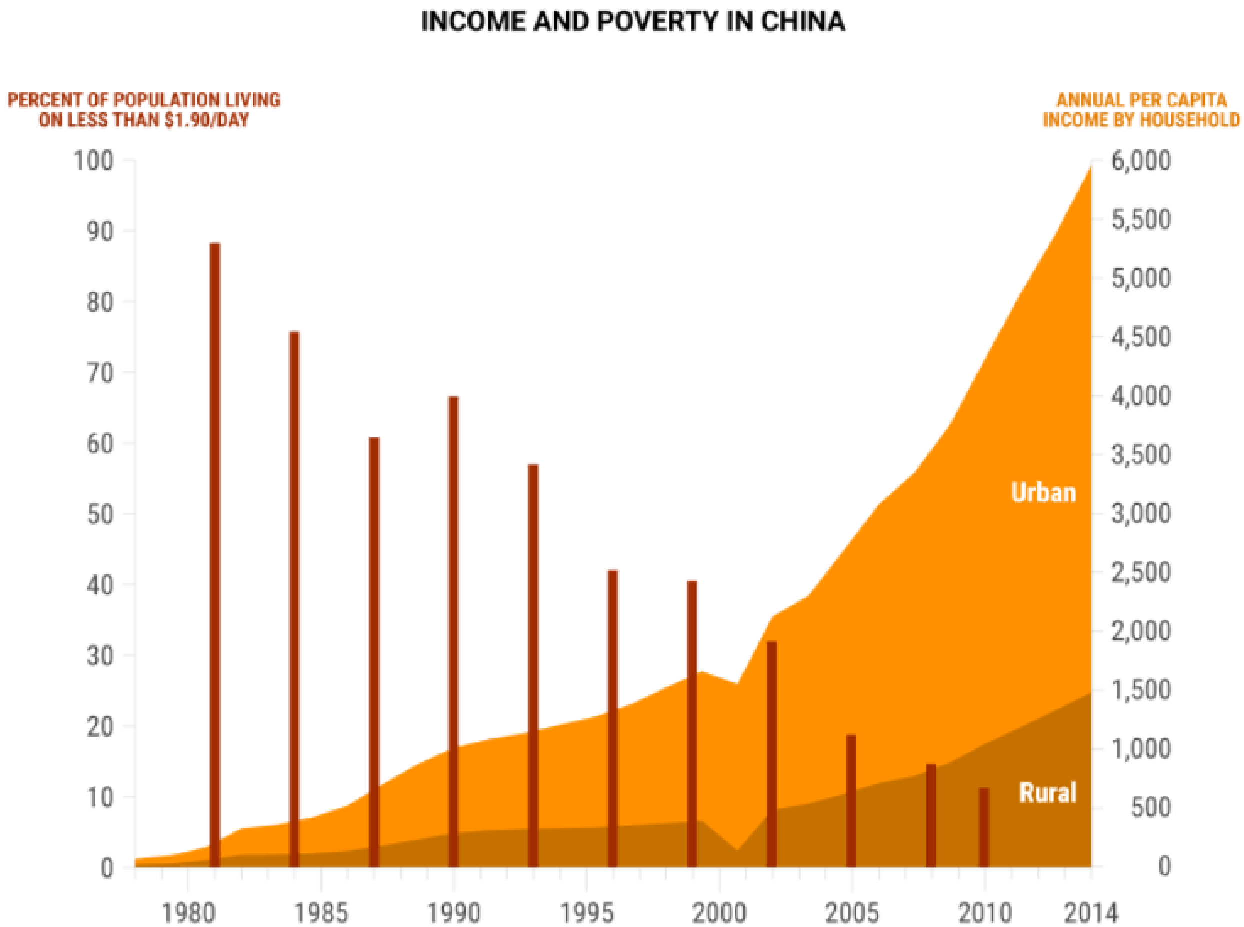
Although the projected number of individuals with diabetes is expected to grow to 629 million people in 2045, the related healthcare expenditures are only expected to increase 7%. This is due to the fact that growth in diabetes prevalence is expected to occur in low- and middle-income countries, which spend fewer healthcare dollars on diabetes management today[14,18].

Diabetes in China

Thanks to economic prosperity and a long-term vision for national development, China is rising to be a global economic competitor with parallel success in the form of longer life expectancy and nearly full healthcare coverage for its population. At the same time, China has come to face accompanying challenges, including escalating healthcare costs and growing inequity in distribution of health resources between urban and rural populations. Although great progress has been made in moving a majority of those who meet the World Health Organization's definition of poverty to a higher economic status, much of China's population still relies on humble means (Figure 1.4). The population of China is, nonetheless, aging, and in

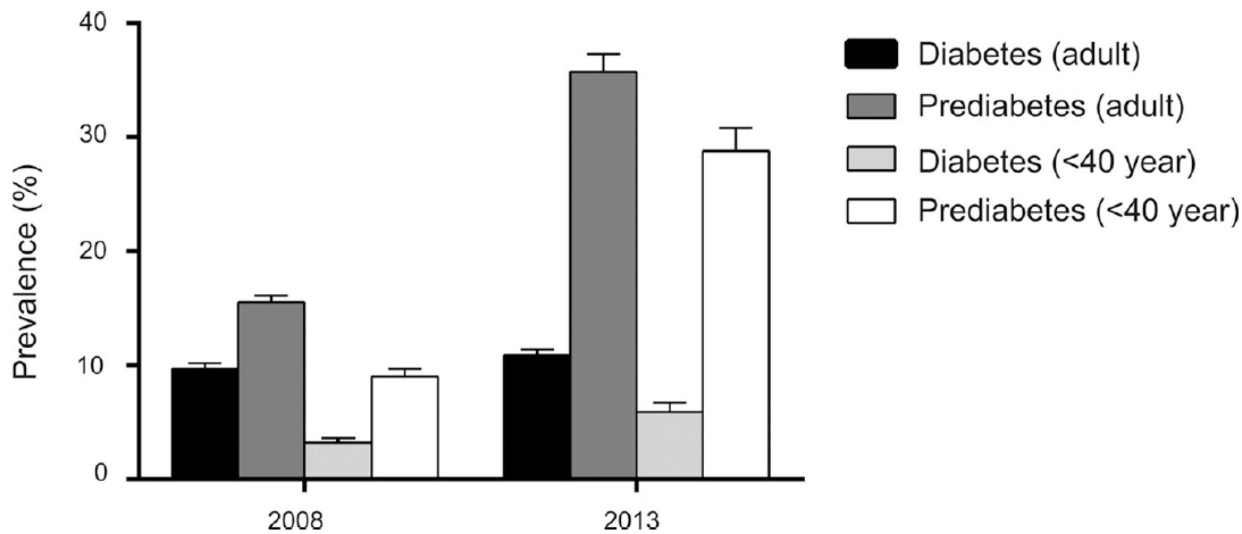
2053, China is expected to have 487 million senior citizens, with over 70% of the population living in urban communities. This shift in demographics—accompanied by rapid urbanization and rising income inequality—makes the problem of chronic disease prevalence and burden of out-of-pocket expenditures to manage these conditions substantially more prevalent[35].

Figure 1.4. Income and Poverty in China[36]



As previously mentioned, China ranks number one in diabetes prevalence. A national survey published in JAMA found diabetes prevalence in China to be 10.9%. This figure, substantiated by the International Diabetes Federation, translates to 114.4 million people[37,14]. This prevalence is 16 times higher than that reported in the first Chinese national health survey conducted in 1980[38]. In addition, 35.7% of China's population meet the criteria for pre-diabetes, implying that an additional 374.6 million people could be at high risk for developing diabetes if unaddressed[37]. China also has the world's most diabetics older than 65, currently 34.1 million individuals, and is expected to balloon to 67.7 million by 2045[14]. In China's younger population, Type 2 prevalence nearly doubled between 2008 and 2013 (Figure 1.5). This cohort also had high A1C and higher rates of complications over time than those with late onset disease[16]. Although there is evidence of variance in genetic risk among ethnicities within China, lifestyle changes accompanying economic growth, coupled with poor health education and an aging population, have been cited as key contributors to the rise in diabetes prevalence[37,39].

Figure 1.5. Prevalence of Diabetes and prediabetes among Chinese individuals <40 years of age[16]



A similar upward trend is seen in diabetes-related healthcare expenditures in China. China spends a total of $110 billion USD annually on diabetes, accounting for over 50% of the diabetes-related healthcare expenditures in the Western Pacific region[14]. A study conducted in 2017 reported that age- and sex-adjusted spending for people in China living with diabetes is 3.4 times more than those without disease[40]. It has been noted, however, that only 32.2% of patients with diabetes were self-identified as being treated for the condition, and of those patients, fewer than half (49.2%) were achieving their glycemic goals. These trends also vary within rural vs urban residence and associated access to care[37,16].

The majority of China's population has some health care coverage under one of China's three main insurance offerings: Urban Employee Basic Medical Insurance (UEBMI), Urban Residence Basic Medical Insurance (URBMI) and Rural New Cooperative Medical Schemes (RNCMS). UEBMI is mainly funded through employee payroll tax, whereas URBMI and RNCMS are both government subsidized. Although UEBMI is a comprehensive coverage plan, most citizens are insured under URBMI or RNCMS, which limits coverage to inpatient service and some pre-specified outpatient services. This makes both prevention and day-to-day management of chronic conditions a personal financial burden for many Chinese. Individuals insured with UEBMI have been noted to have higher expenditures than both URBMI and RNCMS, however this may be linked to not only expanse of coverage, but also where individuals are seeking care[40,41].

Even within these insurance schemes, there is further variability in coverage of procedures, drugs and devices within and between provinces and cities in China. This variability is due in part to China's complex coverage, payment and procurement process. In the case of medical devices for example, technologies are first classified by the National Development and Reform Commission as implantable or consumable. Once a device has been classified, manufactures can apply for coverage at the provincial level by filing individual applications with the local Ministries of Health. Each provincial ministry, and accompanying pricing bureau, sets a maximum price for the product, which then triggers further local assessment of budget impact and fit within provincial insurance schemes. If a product is listed at the provincial level, then city officials have the final decision rights on whether it should be covered at the city level. As available budgets vary by province and city, it is possible that adjacent province or cities may have significantly differing coverage for health technologies[42].

China has three tiers of hospitals, including tier 3 (tertiary), tier 2 (secondary) and tier 1 (primary or community health centers). At the extremes, tertiary hospitals tend to be large, academically affiliated institutions set in urban areas, whereas community health centers are generally more broadly distributed. The three tiers differ in function (i.e., types of procedures), technology, quality of care and scientific management. A survey conducted to assess management of noncommunicable disease in China found that significantly more urban residents received diabetes treatment than rural residents (41.8% vs 27.6%)[16]. Expenditures for high-income urban residents also tend to be higher. Income has been correlated with longer-term therapy strategies, as it may be able to bridge out-of-pocket coverage gaps[34].

Recognizing the local burden and global trends in containing noncommunicable diseases such as diabetes, China has taken numerous legislative steps to address environmental risks, such as tobacco control and expansion of healthcare access to rural communities and underserved communities (i.e. URBMI and RNCMS). Most recently, China has proposed the "Medium-to-Long Term Plan of China for the Prevention and Treatment of Chronic Diseases (2017–2025)," which includes 8 specific strategic measures (Table 1.1)[43]. With regard to diabetes, much of the country's focus has been on monitoring and surveillance programs[41].

Table 1.1. Strategic Measures of China's Medium-to-Long Term Plan for the Prevention and Treatment of Chronic Diseases

Strategy	Goal
Promote health education	*Boost national healthy quality*
Enforce early diagnosis and treatment	*Lower the morbidity risk of high-risk groups*

Reinforce standardized treatment	*Improve therapeutic effects*
Facilitate the cooperation between medical treatment and prevention	*Achieve comprehensive healthcare management*
Refine medical security policies	*Effectively reduce the public's medical burden*
Control risk factors	*Construct a healthy supportive environment*
Arranging social resources in an innovative way	*Drive the development of the healthcare service industry*
Bolster technological support	*Enhance monitoring, evaluation, and innovation in research and development*

In the World Health Organization's first Global Report on Diabetes (2016), the Director General remarked "…in many settings the lack of effective policies to create supportive environments for healthy lifestyles and the lack of access to quality health care means that the prevention and treatment of diabetes, particularly for people of modest means, are not being pursued." If unmanaged, diabetes can be life-threatening and place an enormous economic burden on individuals and health systems. In end-stage diabetes, insulin replacement becomes a compulsory part of disease management, so that when access to care is impeded, patients are rendered perilously vulnerable[44].

Although substantial research has been, and continues to be, conducted on healthcare policy and pharmacotherapy for diabetes management and glucose control, to date little attention has been paid to secondary factors, such as drug delivery technique and associated complications that may help optimize efforts to reach glycemic control.

Role of lipohypertrophy in diabetes management

In the past, limited attention was given to the importance of insulin-injection practices in the management of diabetes. In recent years, this has changed, with greater awareness of injection-related complications, specifically Lipohypertrophy (LH). LH is an avoidable clinical complication affecting insulin injecting diabetes patients. It is a condition that is believed to result from repetitive use of an insulin injection site or lack of injection site rotation. LH presents as a firm lump, or raised mass, which results from the abnormal accumulation of fat at the injection site. Aside from the potential disfigurement caused by the condition, LH tissue impedes insulin absorption, which can lead to significant glycemic variability[45]. In 2016, the first temporal relationship was established between injecting into a LH lesion and glycemic variability in a controlled setting[46].

The injection technique questionnaire (ITQ), conducted among 13,289 insulin-injecting patients from 423 centers in 42 countries between the years of 2014 and 2015, demonstrates that LH is underdiagnosed. The survey also indicates that individuals with LH used more insulin per day and had higher A1c levels than insulin injectors without indication of LH. This group of patients (i.e., patients with LH) also had a higher prevalence of hypoglycemia and recorded glucose variability. In addition to poor detection, the ITQ survey indicated that almost half the respondents reuse needles for reasons of convenience and cost. The practice of needle reuse was correlated with LH and glycemic variability[47].

The findings of the ITQ were not directionally dissimilar to other literature on this subject, however, LH prevalence data has shown to vary across regions (see Section 2). The clinical implications of LH are broad. Nearly 40% of patients with LH experienced unexplained hypoglycemia and nearly half experienced glycemic variability. Comparatively, fewer than 7% of the general insulin injecting population experienced either complication[48]. Glycemic variability, or swings in blood glucose levels, has been associated with various types of neuropathy. There is also evidence to suggest that glycemic variability may be harmful to cardiovascular health in high-risk Type 2 diabetes patients. It is important to note that although these correlations have been observed in both prospective and retrospective research, replicability of the results remains an issue. There are a number of studies that have not been able to demonstrate the same strength in relationships. A conclusion that the research does draw is that the nervous system may be vulnerable to regular fluctuations in blood glucose[49].

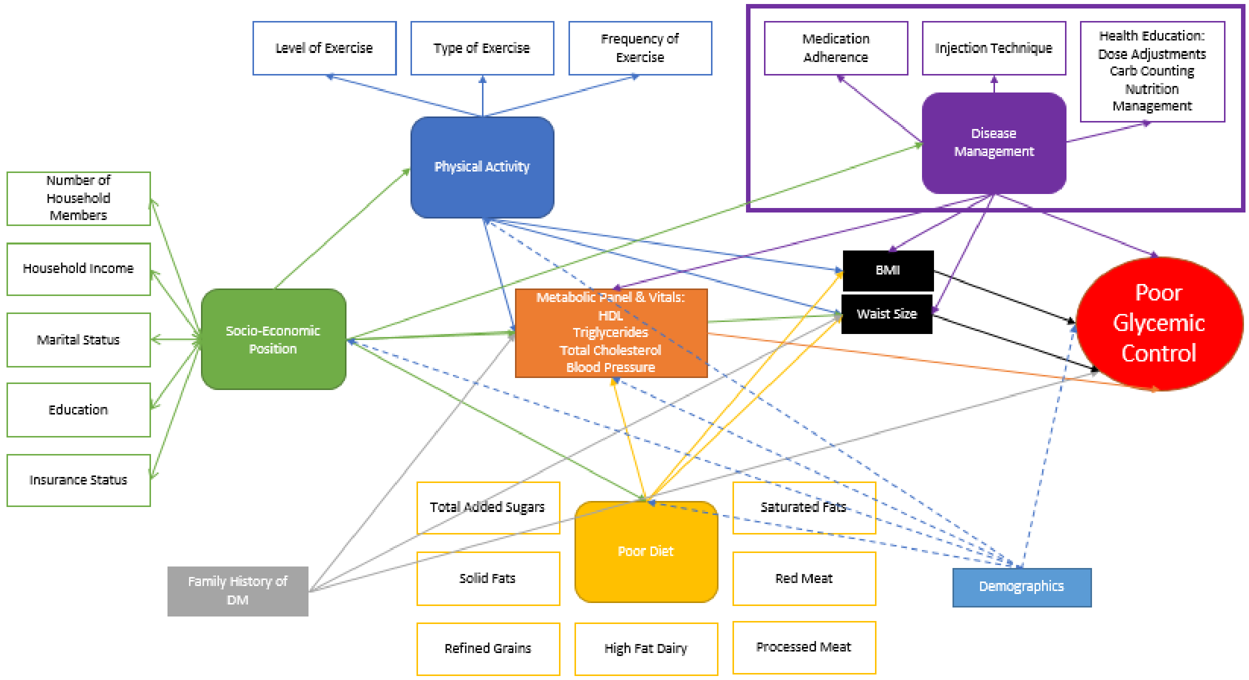
Although the significant costs of hypoglycemic events —driven by ambulance calls, unplanned hospital admissions, and indirect costs associated with missed workdays or loss of work productivity—are well documented, LH costs have largely not been investigated, and remain essentially unknown. (In England, the economic burden of hypoglycemia-related emergency calls totaled £13.6 million per year[50], and average costs of hypoglycemia-related hospitalizations in Germany, Spain and the UK were €533, €691 and €537, respectively for patients with Type 2 diabetes and €441, €577 and €236, respectively for patients with Type 1 diabetes.)[51]. A direct and meaningful cost, directly linked with LH, is the cost associated with excess insulin consumption. Individuals with LH inject on average 15 more units of insulin than those patients with without LH. In Spain, this excess insulin consumption translated to a potential incremental insulin expense of €122 million per year to the Spanish Healthcare System[48].

LH and its associated burden is avoidable. Proper site rotation has been demonstrated to have the greatest protective effect against LH formation[48], and LH avoidance when injecting (among patients with LH) has shown to reduce A1c. Avoiding needle reuse when injecting insulin is also believed to reduce the risk of LH, and is a part of the proper injection technique recommendation[52].

Although research in this area is still emerging, the global burden of diabetes continues to be daunting in both qualitative and quantitative ways. In the case of LH, proper injection technique education is seemingly the solution. Healthcare workers' awareness of the burden, along with reimbursement policies aimed at reducing PN reuse rates, may play a critical role in solving the problem.

Compiling valid evidence of device-specific adherence is essential to developing interventions, however the bulk of research has focused on the burden of non-adherence to medication. Non-adherence, with respect to medication, is defined as failure to take medicines as prescribed. In the US and around the world, the burden of non-adherence is estimated to be in the billions. Policy-based solutions, which include improved access, patient incentives and reporting, have been proposed to achieve adherence goals[53,54]. In the case of LH, studies have highlighted access problems—to an adequate supply of PNs—as a possible barrier for proper injection practices, specifically single-injection use as indicated[55]. Figure 1.6 illustrates how diabetes management, including adherence, injection technique and education, may play an integral role in diabetes outcomes.

Figure 1.6. Disease management modification to Bardenheier's pathway to prediabetes[56]



China is the most populous country in the world and has the most diabetic patients, with a corresponding healthcare burden that is only expected to rise. With these challenges at the forefront of its legislative agenda, the country would stand to benefit from modifications to existing practices that could maximize current investment while delivering against China's population health agenda. Type 1 patients are insulin dependent at the time of diagnosis and Type 2 patients will grow to be insulin dependent at the late stages of the disease. Insulin management is known to be costly and has recently been found to have delivery-related complications, such as LH, that impede optimal absorption and metabolism, impeding A1c control[46]. Correct injection practices are an important factor in achieving glycemic targets. Thus, greater understanding of the effect of injection practices on patient outcomes could prove beneficial to patients and the broader system[57,58]. To provide advice on the potential benefit of addressing LH in the Chinese population, or the necessary access and health education modifications required to help these patients, local evidence is needed.

The only study to consider the burden of LH in China was a self-reported survey conducted in 2010. This survey of 380 diabetes patients demonstrated an overall prevalence of 35.26%, which was significantly correlated with the reuse of insulin pen needles. That study provided insight to the poor state of injection practice and the potential magnitude of the problem in China, however limitations of the approach include self-report bias, lack of clinical confirmation of LH, and no data on insulin waste, cost, or reimbursement policy implications[55].

This research aims to address the gaps in the LH literature in China. Efficacy of insulin therapy is dependent on proper insulin administration. To understand whether further investment in injection-technique education may improve patient outcomes and reduce economic healthcare burden in China, evaluation of current injection practices, establishment of LH prevalence, and assessment of inter-province variability in reimbursement policy for insulin PN and patient outcomes must be investigated.

Specific Aims

The aims of this research are as follows:

Aim 1: Characterize the insulin injecting diabetic population and estimate the prevalence of LH in China

- Describe clinical and economic characteristics of diabetic patients injecting insulin;
- Establish a baseline for current insulin injection practices;
- Determine the direct costs for diabetic patients injecting insulin;
- Estimate the clinician verified prevalence of LH lesions;
- Compare insulin consumption among those patients with and without LH.

Aim 2: Explore the relationship between presence of pen needle reimbursement (PNR) policy, injection practices, clinical outcomes and direct costs among insulin injecting diabetics in China

- Evaluate the relationship between presence of PN reimbursement and *injection site rotation.*
- Evaluate the relationship between presence of PN reimbursement and *LH prevalence and A1c.*
- Evaluate the relationship between presence of PN reimbursement and *health resource utilization and medical expenditures.*

Primary data collected from a cross-sectional observational study conducted in partnership between Becton Dickinson and investigators from Southeast University Affiliated Zhongda Hospital, Chongqing Medical University No.1 Affiliated Hospital, Peking University People's Hospital, and Zhengzhou University No.1 Affiliated Hospital was used to achieve these aims. Laboratory, clinician and patient self-reported data was used to describe the Type 2, insulin injecting, diabetic patient population in China, and to examine the relationship between LH, access to care and patient outcomes (*refer to Data Sources*).

SECTION 2: LITERATURE REVIEW

The prevalence of diabetes, as well as approaches to diabetes and related cost management, has been well documented around the world and continues to be a focus of the research community. Although the occurrence of LH, a complication of insulin delivery, among diabetic patients has been recorded in the scientific literature for decades, only recently has there been a focus on understanding the potential repercussions of LH on the management of diabetic patients and health economies.

To better understand the condition, its prevalence and impact, a PubMed abstract and title search was conducted on full-text Medline literature through June 2018 using the search terms LH and diabetes, resulting in 74 articles. A secondary search was conducted using the combined search terms LH and prevalence, resulting in an additional 8 articles. Article bibliographies were also reviewed for additional relevant literature. References were limited to human studies reported in English. Article titles and abstracts were screened for relevance and further examined for applicability to the research questions.

Eligible studies addressed the topic of LH in conjunction with insulin administration via injection in the diabetic patient population. Excluded studies were those addressing alternative routes of insulin administration (e.g., infusion or syringe), lipodystrophy in conjunction with HIV/AIDS, or as a dermatologic condition independent of diabetes management and independent case studies. Studies exclusive to pediatric patients were also excluded, as the research dataset does not address this patient population. Hypoglycemia and increased insulin consumption were noted as costable complications associated with LH, and were further explored in the literature. A total of 32 studies were included in this analysis.

As noted earlier, the injection technique questionnaire (ITQ)is the most substantial source of literature available on the subject of insulin-injection practices and LH. The survey demonstrates underdiagnosed increased insulin consumption, and higher A1c levels than insulin injectors without indication of LH. LH patients in this study also had a higher prevalence of hypoglycemia and glucose variability. The survey also demonstrated the significant prevalence of needle reuse among the population, and was able to further establish the self-reported causation to be both convenience and cost. The practice of needle reuse was correlated with LH and glycemic variability[47].

LH prevalence data has shown to vary across studies and across regions. In 2013, Blanco et al. demonstrated a 64.4% LH prevalence (76.3% Type 1, 56.1% Type 2) among insulin injecting patients in Spain. The study also indicated a statistically significant relationship between LH and inadequate injection-site rotation, further suggesting that needle reuse may also increase the chance of LH development (not significant)[48]. In 2014, a 346 patient, 18 center, study in Italy showed an LH prevalence of 49.1%, which was further substantiated by a 2018 estimate of 42.9%[52,59]. Additional studies in Germany, Ethiopia, Jordan and Turkey have demonstrated a total LH prevalence of 24%, 31%, 37.3% and 48.8%, respectively[60-63]. The ITQ found a global LH prevalence of 30.8% among patients who were examined by trained nurses[47]. See Table 2.1 for full review of LH prevalence[64].

Table 2.1. Lipohypertrophy prevalence in diabetic patients using insulin pens or syringes

Study		Sample Size	Geography	Type 1 & 2 (%)	T1 (%)	T2 (%)
McNally et al.	1988	281	United Kingdom	27.1		
Hauner et al.	1996	279	Germany	24	28.7	3.6
Seyoum et al.	1996	100	Ethiopia	31		

Ibarra et al.	1998	150	Spain	52		
Partanen et al.	2000	100	Finland		29	
Wallymahmed et al.	2004	74	United Kingdom		44	
Varder et al.	2007	215	Turkey	48.8		
Hajheyadari et al.	2011	220	Iran	14.5		
Cunningham et al.	2013	55	Ireland	51		
Blanco et al	2013	430	Spain	64.4	76.3	56.1
Grassi et al.	2014	346	Italy	48.7		
Ji et al.	2014	380	China			35.3
Ajlouni et al.	2015	1090	Jordan			37.3
Berard et al.	2015	503	Canada	24.6		
Frid et al.	2016	13289	Global	30.8		
Li et al.	2016	736	China			73.4
Patil et al.	2016	225	India	11.1		
Hernar et al.	2017	215	Norway		63	
Pozzuoli et al.	2018	352	Italy	42.9		

In total, the articles relating to LH prevalence in this review represented over 19,000 patients (disproportionately ITQ) across 45 countries. Definition of LH among all studies showed minimal variability. Most referenced visibility, palpability and location of the lesion as defining factors of LH. The most accurate method of LH detection was noted to be via ultrasound; however, the method can be costly and time consuming, and was only incorporated into one study[48,64]. Recent studies (with the exception of the Iran and India studies) reported higher rates of LH prevalence than earlier studies. In those studies reporting complications, patients with LH had higher occurrences of both unexplained hypoglycemia and glycemic variability than those without LH. They also demonstrated higher economic burden due to greater insulin consumption. The prevalence estimates, however, varied greatly across studies from 3.6-76.3% (Table 2.1). Study quality, LH detection approach and investigator training may account for some of this variability.

Most studies relied on a combination of manual detection and visual confirmation to determine the presence of LH. Few studies, however, offered a detailed description of investigator training in LH detection or method of observation and evaluation[65,66]. As manual detection through palpation is the most common and practical approach, granularity in describing these methods will support the standardization necessary for comparability in future LH research.

Moreover, not all studies described the qualifications of the researchers tasked with detecting and recording the presence of an LH lesion. Variability in training and experience among these professionals both within and between studies may compromise the validity of the assessment and limit comparability across studies. Study investigators should not only follow a uniform process for detection and confirmation to ensure accuracy in reporting, but should also control for years of investigator experience in their analysis to ensure that there is no inter-study variance among research staff. Instances of patient self-report were few, but did demonstrate over-reporting when confirmed by a trained medical professional[47].

LH was commonly associated with needle reuse, injection frequency, and incorrect injection site rotation. Incorrect injection site rotation was the most commonly cited risk factor followed by needle reuse; nonetheless, a standard definition for site rotation did not appear in the literature until recent years. Needle reuse has been correlated with pain, cost and convenience.

Lack of injection site rotation has been most commonly correlated with pain avoidance and patient education[52,48,47,63].

The heterogeneity of this research makes drawing conclusions across multiple studies a challenge. Parameters such as needle gauge and needle length have also been positively correlated with LH or its predictive factors[47]. However, studies of needle qualities do not control for such factors as duration of diabetes or duration of insulin exposure, which may confound the relationship between recent innovations in PN technology and LH prevalence. These and other unexamined factors, such as health literacy, diet, culture and access to healthcare, could all contribute to the risk for LH. Appropriate data is currently unavailable to examine these relationships[64].

To address the issue of LH, the scientific community must have a keen understanding of LH-influencing factors and a dependable estimate of LH prevalence. Much of the substantial work in this area has occurred in parallel over the past decade. Future research will now be able to build upon the knowledge and gaps in methodology applied to date.

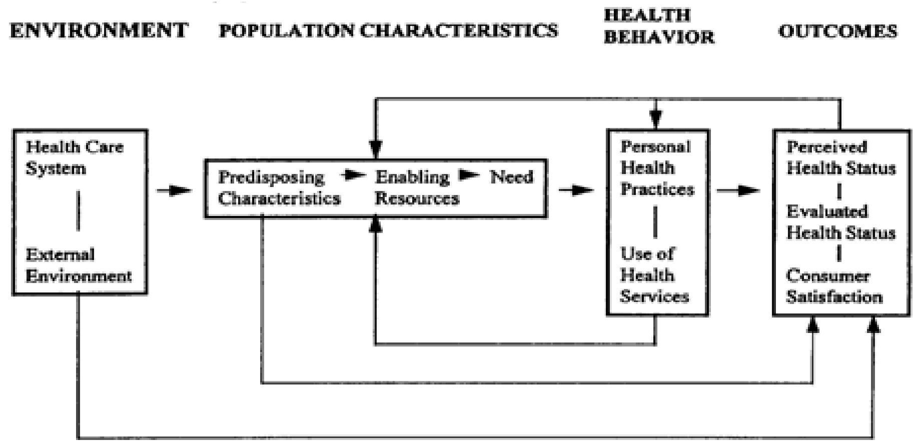
SECTION 3: METHODS

Conceptual Framework

Among the most commonly used conceptual frameworks of health resource utilization is the Anderson Framework. This framework, which has evolved over many iterations to explain drivers of patient behavior and choice, was originally developed to predict and explain the use of health services. It was developed from the study of the family as a single unit of measurement, but progressed to the study of the individual as a unit of measurement to address the heterogeneity of the family variable. The framework further evolved to consider systematic concepts of care and satisfaction as outcomes. Today the framework integrates outcomes as an endpoint and includes a feedback loop to demonstrate the implications of outcomes on individual beliefs and future choices (Figure 3.1)[67].

The Andersen framework introduces mutability of predictive factors as a critical distinction in understanding resource utilization. Mutability refers to how easily a factor can be changed. A person's demographic attributes are fixed and thus immutable, however, enabling factors, such as insurance status, can be altered and are thus mutable. In the case of LH reimbursement policy, PN reuse and injection practices are mutable factors. The framework also distinguishes *potential* access from *realized* access, highlighting that potential for accessing care is influenced by the presence of enabling resources. Further, there is also a distinction between equitable and inequitable access, where equitable access is defined by immutable factors (e.g., demographic attributes) and inequitable access is an outcome influenced by circumstance (e.g., social structure or enabling resources)[67].

Figure 3.1. Andersen Framework of Healthcare Utilization[67]



Component	Factors
Health Care System	Policy, Resources, Organization
External Environment	Physical, Political, Economic components
Predisposing Characteristics	(Demographic) Age, Gender (Social Structure) Education, Occupation, Ethnicity (Health Beliefs) Attitudes, values, and knowledge about health and health services
Enabling Resources	Income, Health Insurance, Regular Source of Care, Travel & Waiting Times
Need	Perceived, Evaluated (i.e. Physician Dx)
Use of Health Services	Type, Site, Purpose, Time Interval
Personal Health Practices	Diet, Exercise, Health Education
Health Status	Perceived, Evaluated
Consumer Satisfaction	Convenience, Availability, Financing, Provider Characteristics, Quality

This framework presents health resource utilization as a sequence of access parameters, all of them in turn affected by environmental or systemic factors. Individuals' predisposing factors influence their propensity to use more or less healthcare. Their enabling factors influence their ability to seek and acquire care. Finally their level of need, or severity of illness, whether perceived or defined, drives the action. The framework also allows the outcome to determine the individuals' probability of engaging in future health resource utilization behavior. This feedback loop in the framework suggests that a positive or negative outcome may influence patients' predisposing belief about healthcare[67]. The relationships highlighted in the Andersen framework are logical, however not actionable in the context of data available for this research. The framework does, however, offer a way to analyze the directionality of the effect following a change in individuals' predisposing or enabling factors to the extent that they can be measured in this study. For example, if a patient's diabetes is severe, then the Andersen framework predicts that that patient is more likely to use healthcare services, all else being equal. This framework should allow for an intimate analysis of the relationship between predictive variables and the dependent outcomes of health resource utilization in this research

Design

This is a cross-sectional study of observational data. Further information on the design and methods is provided in the Data Source section below and in Ji et al. 2017 and 2018[68,69].

Study Population

Eligible study participants included individuals who received a clinical diagnosis of diabetes mellitus Type 1 or Type 2 and were receiving insulin therapy at the time of the study. Participants must have been administering insulin via pen and PN continuously for a period of at least 1 year. Other inclusion criteria included being between the ages of 18 and 80 years, having a BMI $\geq$18.5 kg/m^2, and being able to confirm that they were able to understand the investigator's questions and complete the study questionnaire independently. All participants provided informed consent prior to participation.

Patients who do not self-inject or those taking insulin via pump or syringe were excluded from the study. Patients whose injection sites may have been compromised via a known cause such as surgery or other trauma, skin disorders (e.g., psoriasis, lupus, etc.) or skin imperfection/anomalies (e.g., discolorations, tattoos, or other abnormalities) were also excluded. Finally, individuals with diseases that would reduce the survival of red blood cells (e.g., sickle cell anemia, thalassemia, etc.) were also excluded, as these conditions may compromise reliability of HbA1c results.

Data Source

The data for this study were collected through a multi-center observational study conducted at university hospital (Tier 3) clinics in Beijing, Zhengzhou, Chongqing, and Nanjing between December 2, 2013 and January 27, 2014; the former two sites were located in provinces that did not provide reimbursement for insulin PNs, whereas the latter two had provincial PNR policy in place. Sequential patients attending the clinics were invited to participate in the study.

Participants completed a questionnaire which included questions on demographic attributes and medical history, diabetes history, injection history, injection technique training and practices, frequency of hypoglycemia (self-reported), health resource utilization, employment, and income status. Upon completion of the questionnaire, patients underwent a structured physical exam of height and weight, visual inspection and palpation of all injection sites, and HbA1c testing. Study staff who performed physical examinations were trained to detect LH, first with models or mannequins, and then with patients known to have LH lesions.

Data Limitations

The data have several limitations, including those commonly associated with cross-sectional study design. Patients' healthcare utilization (i.e., outpatient clinic visits and hospitalization) was solicited in the survey via self-report over a recall period of 6 months, potentially introducing recall bias. Total healthcare costs associated with inpatient stays, outpatient visits, and insulin use were not directly solicited from participants, possibly masking true variability in costs between settings of care. Unknown factors affecting quality of care and patient outcomes may have been missed. Variability in scope of PN reimbursement policy including number of needles covered per insulin prescription, needle length or type, and coverage for other factors of diabetes management was not captured and may confound observed relationships. And lastly, the patient population only represents those from endocrinology clinics from a small sampling of tertiary hospitals in China, threatening external validity. The study limitations section provides an in-depth analysis of the implications of these limitations.

Measures

Lipohypertrophy is measured in 3 ways: (1) presence (i.e., prevalence) is a binary variable (0 = LH not present; 1 = LH present); (2) number indicates a count of LH nodes; and (3) length of longest LH node, in millimeters.

Several pen needle-related variables are measured. Receipt of instruction in insulin injection is a binary variable, where 0 = no; 1 = yes. Recency of instruction (either receipt or review) is a categorical variable with the following responses: within 6 months; between 6 and 12 months prior to the survey date; 1 – 2 years prior; more than 2 years prior; 2 – 5 years prior; 5 – 10 years prior; more than 10 years prior. Rotation of insulin injection site is a binary variable, where 0 = no and 1 = yes. Re-use of pen needles is a binary variable, where 0 = no and 1 = yes, and a categorical variable that measures degree ($0 < \text{times} < 2$; $2 \leq \text{times} \leq 6$; $7 \leq \text{times} \leq 14$; $15 \leq \text{times} \leq 28$; $\text{times} > 28$). Average number of times a pen needle is re-used is a continuous variable. The value for participants who do not reuse pen needles is set to zero by the investigator. Daily number of daily injections is a count variable. Insulin type is measured by a dichotomous variable (0 = other; 1 = twice-daily premixed insulin). Needle length is a categorical variable measured according to standard pen needle lengths (4 millimeters, 5 millimeters, 6 millimeters, 8 millimeters). Injection area size is a measure of the approximate dispersion region of injections on the abdomen. Categorical responses, designed to be ordinal, are stamp, credit card, playing card, and postcard.

Diabetes-related health resources utilization is represented by a number of variables. Diabetes-related outpatient care is measured by number of visits (count variable) in the previous 6 months, and outpatient costs, in RMB, calculated based on 374.1 RMB per outpatient visit. Diabetes-related hospital stay is a binary variable (0 = no; 1 = yes) that measures whether a participant was hospitalized in the previous 6 months for a condition/complication related to diabetes. Inpatient costs are calculated for patients who were hospitalized in the previous 6 months based on 6581 RMB per hospital stay. The cost values for participants who did not report diabetes-related outpatient service use or a hospitalization is set to zero by the investigator. Insulin costs are calculated based on responses to average daily number of units, with costs calculated based on 0.25 RMB per unit of insulin. Out-of-pocket costs are self-reported by participants. Patients were dichotomized into lower- and higher-cost patients. Total 6-month diabetes-related cost comprises the sum of outpatient and inpatient services. Patients with total 6-month costs at the 75th percentile or above were categorized as having "high" costs while those with total costs below the 75th percentile were classified as having "lower" costs. This cutoff was determined through an evaluation of the distribution of the data, which suggested that costs for these patients increased substantially upon reaching the 75th percentile.

Participant age is a continuous variable, measured in years. Gender represents biological sex, and is coded as 0 = female (referent); 1 = male. Education level was collected as a 6-category variable (primary school or below; junior school; high school; bachelor's degree; master's degree; other), but was dichotomized for analysis, so that 0 = bachelor's degree or higher (referent); 1 = high school or less education. Annual income was collected via a 7-category response (no income; $0 < \text{RMB} \leq 1000$; $1000 < \text{RMB} \leq 3000$; $3000 < \text{RMB} \leq 5000$; $5000 < \text{RMB} \leq 10000$; $10000 < \text{RMB} \leq 25000$; $\text{RMB} > 25000$), but was modified to a 3-level categorical variable (because of low frequency responses in some categories) from which three binary dummy variables were constructed: no income (referent); 0 < RMB ≤ 3000; RMB > 3000. Medical insurance was similarly collected via a 6-category response, from which binary dummy variables were created: urban employee medical insurance (referent); urban resident medical insurance; new rural cooperation medical insurance; free medical insurance; other medical insurance; more than 1 type of medical insurance. Pen Needle reimbursement is a binary variable, where 0 = has some level of PN reimbursement, and 1 = has no level of PN reimbursement. BMI, calculated as kilograms/meters^2, is treated both as a continuous variable and categorical variable, which dummied for analytic purposes: 18.5 < BMI < 24; 24 ≤ BMI <28; BMI ≥ 28.

Diabetes-related complications and other comorbid conditions are measured by binary variables indicating presence of the condition. In all cases, 1 = presence of complication/condition, and 0 = absence. Variables comprise: retinopathy, nephropathy, neuropathy, other diabetes-related complications, myocardial infarction (MI), cardiovascular disease (CVD), and hyperlipidemia.

Diabetes type is a binary variable, and is coded as 0 = Type 1 (referent) and 1 = Type 2. Duration of diabetes and duration of insulin therapy are both continuous variables, measured in years. Daily insulin dose, measured in International Units (IU), and IU per kilogram, are both continuous variables. Glycated hemoglobin (HbA1c) is a continuous variable, measured in percent (National Glycohemoglobin Standardization Programme) and mmol/mol (International Federation of Clinical Chemistry). For analytic purposes it was always dichotomized at its standardized clinical threshold: HbA1c < 7%; HbA1c ≥ 7%. Frequency of hypoglycemia event in the previous 6 months was a self-reported categorical variable that was dummied, according to its original responses, as follows: none (referent); 1 - 2 events; 3 or more events.

Analytic Approach

Aim 1: Characterize the insulin injecting diabetic population and estimate the prevalence of LH in China

Univariate methods were used to characterize the insulin injecting diabetic population in China for the full sample and stratified by LH status. Means were generated for continuous variables, frequencies were run for categorical variables, and applied bivariate methods (i.e., t-test, Wilcoxon Rank Sum test or ANOVA for continuous variables; chi-square test for categorical variables) were used to compare attributes across LH strata. Pearson's correlations were calculated between total daily dose of insulin and both BMI and weight.

Logistic regression was used to analyze the cross-sectional association between LH and explanatory variables, including duration of insulin therapy, number of daily injections, gender, BMI, weight-adjusted insulin dose, HbA1c, site rotation, PN length, PN reimbursement, and frequency of PN reuse. Point estimates of odds ratios and 95% Confidence Intervals (CI) were generated for LH predictors. A stepwise approach, with subsequent point estimates and ORs, was fitted to generate multivariable models.

IMS MIDAS data combined with public and private resources were used to derive unit costs for insulin and healthcare resource utilization in China Unit costs for insulin were estimated to be 0.25 RMB[70]. The 4th China National Health Services Survey conducted by the China Ministry of Health was used to obtain unit costs for outpatient and hospital services[71]. Consumer price index for medical goods in China was used to inflate figures to 2015 RMB (374.1 RMB, outpatient and 6581 RMB inpatient)[72]. Daily insulin costs and the four-week patient out of pocket (OOP) spending were converted to 6-month costs by multiplying the daily insulin costs by a factor of 182 and four-week patient OOP spending by a factor of 6.5. Total 6-month costs were calculated for patients by summing the total costs for outpatient visits, hospitalizations, insulin costs and patient OOP spending for PNs. All costs were inflated to 2015 RMB[69].

Insulin consumption costs were further evaluated by LH status. Differences in insulin consumption were used to assess economic burden of excess inulin required to achieve glycemic control. Cost of excess insulin consumed was calculated by multiplying average excess units used by a standard insulin unit price of 0.25 RMB[70]. This cost of the observed difference in insulin used was then extrapolated to the insulin-injecting population in China[48].

Aim 2: Explore the relationship between PNR policy, injection practices, clinical outcomes and direct costs among insulin injecting diabetics in China

To explore the relationship between PNR policy, injection practices, clinical outcomes and direct costs among insulin injecting diabetics in China, descriptive statistics (i.e., mean, median, SD or 95% confidence interval) were compared for patients with and without insurance coverage for PN using chi-square as well as Student's t-test or Wilcoxon Rank Sum test.

Because the same unit costs are applied for each patient, it is likely that evaluation of the total costs in a regression model will result in artificially low variances and increased Type II error. To reduce the potential for this bias, the effect of PN reimbursement on total costs was evaluated using a logistic regression model that dichotomized patients into lower- and higher-cost patients. Income, education, age, gender, insurance, income, type and duration of diabetes, duration of insulin use, frequency of hypoglycemia in the prior 6 months, BMI, and presence of cardiovascular disease, hyperlipidemia, retinopathy, nephropathy, neuropathy, presence of other complications are included as covariates in the logistic regression.

Statistical calculations were performed using SAS statistical software version 9.2.

SECTION 4: RESULTS

Clinical and Demographic Characteristics of the Sample

Of 403 patients who provided informed consent, 401 completed the study procedures and results are described for them. Clinical and demographic information is provided in Table 4.1. Data are provided for the full sample and stratified by LH status. Patients were nearly 60 years old and 50% male. Patients had diabetes for nearly 12 years, > 93% Type 2, and had been taking insulin for a mean of 5.8 years (range 1-29.3 years). 400 of the 401 patients who completed study procedures also provided reimbursement information. More than 98% of these patients had some medical insurance; 142 (35.5%) had medical insurance that covered a portion of PNs costs. Mean HbA1c was 8.0% (SD 1.7% [64 mmol/mol]) in the study population. Nearly 60% of participants had an occurrence of hypoglycemia in the 6 months prior to the survey. Average BMI was 25.4 kg/m^2, and ranged from 18.8 to 41.4 kg/m2, with ~ 31% between 18.5 and 24 kg/m2, 51% between 24 and 28 kg/m2, and 18% > 28 kg/m2. The largest proportion (49.3%) of the 213 subjects with LH had BMI between 24 and <28 kg/m2. Viewed differently, 56 of the 123 (45.5%) subjects with BMI < 24 kg/m2 had LH, compared to 105/205 (51.2%) with BMI between 24 and <28 kg/m2, and 52/73 (71.2%) subjects with BMI ≥ 28 kg/m2.

Duration of diabetes did not differ significantly between those with and without LH; duration of insulin injection was numerically longer, though not statistically so, in those with LH (p=0.069). LH was present in 19 of 26 (73.1%) subjects with Type 1 diabetes and 193 of 374 subjects (51.6%) with Type 2 diabetes (p=0.034). Compared to patients without LH, those with LH had higher BMI (26.0 vs 24.8 kg/m2), took more insulin daily (38.1 vs 27.1 IU), more weight-adjusted insulin (by 31.7%, 0.54 vs 0.41 IU/kg), and had 0.5% higher HbA1c (8.2% vs

7.7% [66 vs 61 mmol/mol]) (all $p \leq 0.01$). There was a significant positive relationship between BMI and LH prevalence, p =0.002.

Table 4.1. Clinical characteristics: Full Sample and by Lipohypertrophy Status

Measurement	All (N=401)	With LH (N=213)	Without LH (N=188)	p-value
Age, years	59.6 (11.5)	59.8 (11.2)	59.3 (11.9)	0.655
Gender (male)	200 (49.9%)	111 (52.1%)	89 (47.3%)	0.340
Diabetes duration, years	11.8 (7.3)	12.4 (7.7)	11.3 (6.8)	0.145
Type 2 diabetes	374 (93.3%)	193 (90.6%)	181 (96.3%)	0.034
Duration insulin therapy - years	5.8 (4.5)	6.2 (5.0)	5.4 (4.0)	0.069
Daily insulin dose - IU Insulin dose IU per kg	33.0 (18.4) 0.48 (0.26)	38.1 (20.1) 0.54 (0.28)	27.1 (14.3) 0.41 (0.21)	<0.001 <0.001
With medical insurance	98.5%	98.6%	98.4%	1.0
HbA1c (%) HbA1c (mmol/mol)	8.0 (1.7) 64	8.2 (1.8) 66	7.7 (1.5) 61	0.003
Hypoglycemia* occurrence	237 (59.1%)	118 (55.4%)	119 (63.3%)	0.108
BMI (kg/m^2) $18.5<\text{BMI}<24$ kg/m^2 $24\leq\text{BMI}<28$ kg/m^2 $\text{BMI}\geq 28$ kg/m^2	25.4 (3.2) 30.7% (n=123) 51.1% (n=205) 18.2% (n=73)	26.0 (3.3) 26.3% (n=56) 49.3% (n=105) 24.4% (n=52)	24.8 (3.0) 35.6% (n=67) 53.2% (n=100) 11.2% (n=21)	<0.001

Data are N (and percentage). Mean (SD), or median as noted. P-value relates to t-test or chi-square test of difference in attribute between participants with and without LH.
*Hypoglycemia is self-reported within the past 6 months.

Table 4.2 presents diabetes-related healthcare utilization and expenditure data. Nearly two-thirds of the study population reported at least one diabetes-related outpatient (OP) visit (62.7%) and 14.4% of the sample had at least one hospital stay in the previous 6 months. The average number of diabetes-related OP visits and hospital stays per patient was 2.55 (SD 2.55) and 0.177 (SD 0.516) respectively. The average daily insulin dose was 33.95 (SD 18.41), with patients reporting a range from 6 - 118 units per day. The average expenditure on OP and inpatient services over a period of 6 months were 1,058 (1057.7) and 1,291 (SD 3,762.1) RMB, respectively, however diabetes-related hospital costs were reported as high as 43,760 RMB. Average daily insulin costs for this study population were 7.08 RMB. Self-reported OOP costs, over a period of 6 months, were reported between 0 and 3,330 RMB with an average of 289 RMB (284.8).

Table 4.2. Total Diabetes Related Healthcare Resource Utilization

	All
Any DM-related OP Visits (% of total)	252 (62.7)
Any DM-related Hospital Stay (% of total)	58 (14.4)
Number of DM-related OP Visits	
Mean (SD)	2.55 (2.55)
Median (Q1, Q3)	1 (0, 5)
Min, Max	0, 10
Number of DM-related Hospital Stays	
Mean (SD)	0.177 (0.516)
Median (Q1, Q3)	0 (0, 0)
Min, Max	0, 6
Daily Insulin Dose	
Mean (SD)	33.95 (18.41)
Median (Q1, Q3)	30 (20, 42)
Min, Max	6, 118
BMI-Normalized Daily Insulin Dose (n=401)	
Mean (SD)	1.29 (0.68)
Median (Q1, Q3)	1.19 (0.77, 1.69)
Min, Max	0.24, 4.92
DM-Related OP Costs in RMB (n=400)	
Mean (SD)	1058 (1057.7)
Median (Q1, Q3)	415 (0, 2073)
Min, Max	0, 4146
DM-Related Hospital Costs in RMB (n=401)	
Mean (SD)	1291 (3762.1)
Median (Q1, Q3)	0 (0, 0)
Min, Max	0, 43760

Daily Insulin Cost in RMB (n=402) Mean (SD) Median (Q1, Q3) Min, Max	 7.08 (3.96) 6.45 (4.3, 9.0) 1.29, 25.37
BMI-Normalized Insulin Cost in RMB (n=402) Mean (SD) Median (Q1, Q3) Min, Max	 0.28 (0.15) 0.26 (0.16, 0.36) 0.05, 1.06
Reported 6- month OOP Costs in RMB (n=375) Mean (SD) Median (Q1, Q3) Min, Max	 289 (284.8) 220 (114, 381) 0, 3300

Data are N (percentage), Mean (SD), or median as noted.
*OOP is self-reported for 4 weeks and extrapolated to 6 months

Lipohypertrophy prevalence, characteristics, and extrapolated cost

In Table 4.3, we present LH prevalence and characteristics. Overall LH prevalence was 53.1% (95% CI 48.2, 58.0), most commonly found in the abdomen (52.4%), which was used as an injection site by 391 or 97.5% of subjects, followed by the thigh (LH in 15.5%) and arm (9.4%); LH was not present in the buttocks, however only 29 (7.2%) subjects used this area for injections. In participants with LH, 2.3 (SD 2.2) lesions were found on average, and ranged from 1 to 20. The average length of the longest dimension of a lesion was 16.1 mm, with a maximum 80 mm.

Table 4.3. Lipohypertrophy Prevalence, Location, and Lesion Length

	Total	All
Overall prevalence: % of total N (95% CI)	401	53.1 (48.2, 58.0)
Physical Location of LH Lesion among LH patients Abdomen, number (%) Thigh, number (%) Arm, number (%) Buttock (%)	 391 84 64 29	 205 (52.4) 13 (15.5) 6 (9.4) 0 (0.0)

Average Number of LH Lesions Mean (SD) Min, Max		2.3 (2.2) 1, 20
Average Length of LH Lesions, in millimeters Mean (SD) Min, Max		16.1 (13.8) 1, 80

Figure 4.1 presents the relationship between BMI and total daily dose (TDD) of insulin in all subjects. Pearson's r values for correlation were not significant: 0.277 for TDD and BMI; and 0.247 for TDD and weight (kg). Correlations were also assessed separately between BMI and TDD of insulin in subjects with and without LH, with R values = 0.284 and 0.159, respectively (see Figures 4.2 and 4.3).

Figure 4.1. Scatter plot for BMI vs total daily dose (TDD) of insulin in all study subjects
$R = 0.277$, $R^2 = 0.077$

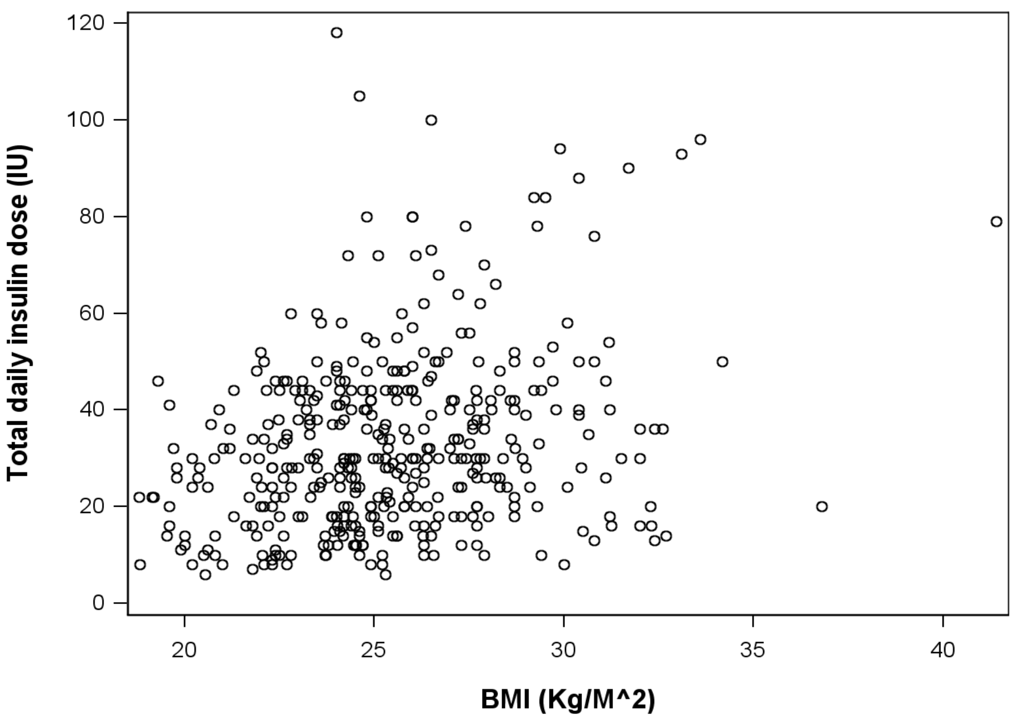


Figure 4.2. Scatter plot for Total daily insulin dose with BMI for subjects with LH
R = 0.284, R^2 = 0.081

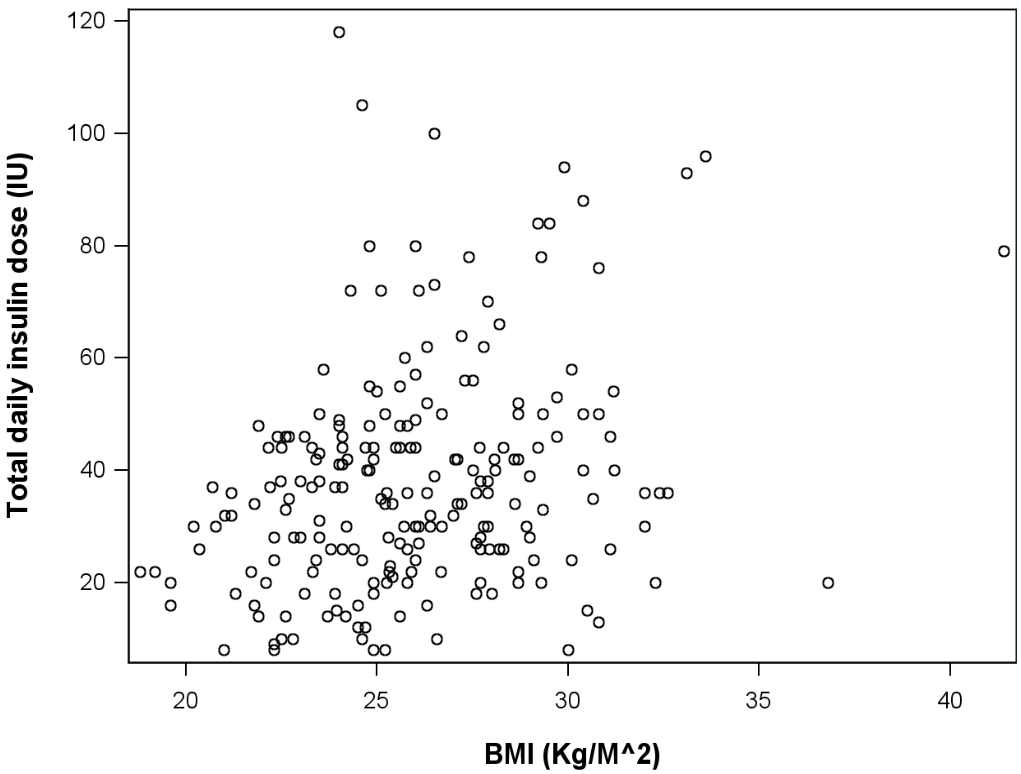
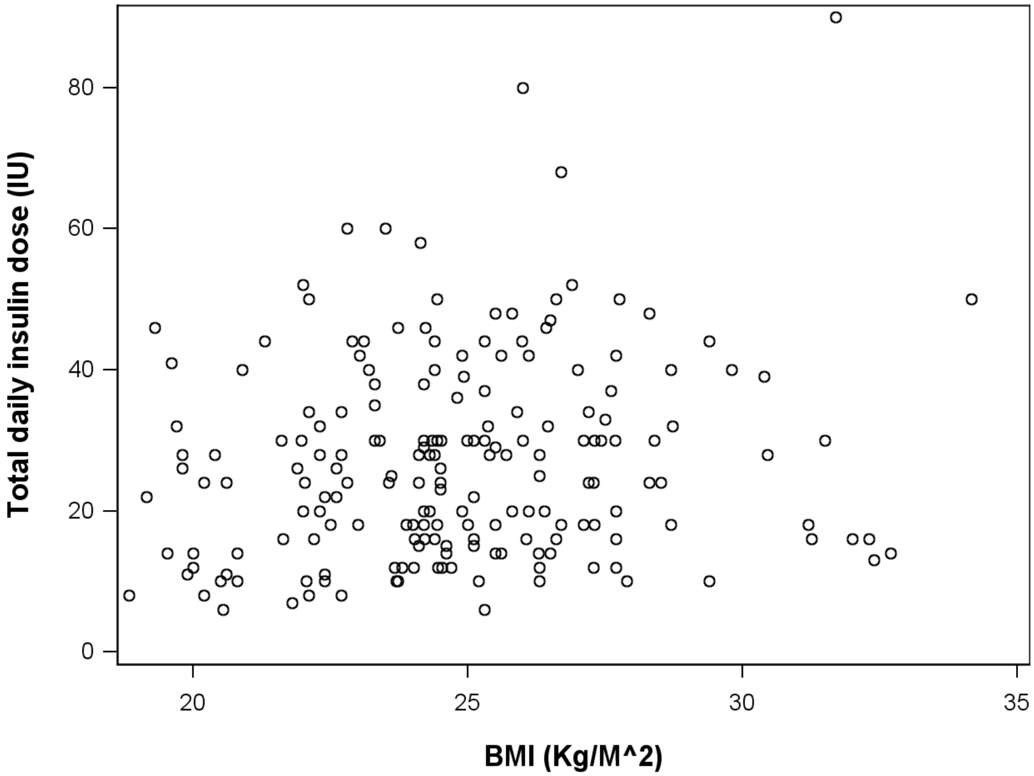


Figure 4.3. Scatter plot for Total daily insulin dose with BMI for subjects without LH
R = 0.159, R^2 = 0.025



A 2014 China IMS report estimated the number of insulin injecting patients to total 9 million[73]. This estimate multiplied by the study established prevalence (53.1%) and an average excess daily consumption of 11IU of insulin in LH patients totals 52,596,000 excess units of insulin consumed by insulin injecting patients with LH in China annually. Total daily costs for insulin of 9.5 (LH) vs 6.8 (no-LH) were calculated using the IMS reported average price of insulin of 0.25RMB per unit[70]. The total cost of excess insulin consumption totaled RMB 4,709,704,500. However, this estimate assumes perfect adherence. IMS data indicated that insulin injection adherence in China is 42% (or 154 injection days)[73]. When adjusting for adherence, the estimated cost of excess insulin consumption in insulin injecting diabetes patients with LH in China is RMB 1.87 billion, or $313 million (2015 USD).

Insulin injection practices

Table 4.4 provides information related to insulin-injection technique. Roughly ninety percent of participants had received some (any) injection training (~15% within the past 12 months), and nearly 97% claimed they rotated their injection sites; correct site rotation was documented in more subjects without LH (93%) than in those with LH (68%), p< 0.001. Needle reuse was common and reported by 95% of patients. Reuse did not differ between those with and without LH; however, median frequency of reuse was significantly greater in those with LH, 13 times vs 7.5 times (p=0.003), with one subject (with LH) who took insulin twice daily reporting use of a single needle for 6 months, or 360 times. Patients with LH took >20% more injections daily than patients without LH (p<0.001). Patients in the study most commonly used 5mm needles (nearly 60%), followed by 6mm, 8mm, and 9.6% who used 4mm. There were no differences between needle length in those with or without LH. In the most commonly used injection site (abdomen), patients reported using a variety of injection size areas – most commonly that of a playing card (nearly 43%). There were marginal differences, although not statistically significant, in the distribution of the size of injecting areas between those with and without LH, p = 0.061.

Table 4.4. Injection Technique-Related Findings

Measurement	All (N=401)	With Lipo (N=213)	Without Lipo (N=188)	p-value
Received training – any Within last 2 years	360 (89.8%) 126 (31.4%)	196 (92.0%) 58 (29.6%)	164 (87.2%) 68 (36.2%)	0.170 0.080
Site rotation correct	318 (79.3%)	144 (67.6%)	174 (92.3%)	<0.001
Needle reuse - Yes	381 (95.0%)	206 (96.7%)	175 (93.1%)	0.096
Needle reuse – frequency (median, Q1-Q3)	10.0 (16.0)	13.0 (14.0)	7.5 (11.5)	0.003

Degree of reuse 0<times<2 2≤times≤6 7≤times≤14 15≤times≤28 times≥29	20 (5.0%) 130 (32.4%) 101 (25.2%) 100 (24.9%) 50 (12.5%)	7 (3.3%) 60 (28.2%) 56 (26.3%) 63 (29.6%) 27 (12.7%)	13 (6.9%) 70 (37.2%) 45 (23.9%) 37 (19.7%) 23 (12.2%)	0.054
Number of injections daily	2.1 (1.0)	2.3 (1.0)	1.9 (0.9)	<0.001
Twice-daily premixed insulin	215 (53.6%)	118 (55.4%)	97 (51.6%)	0.446
Needle length used: 4mm 5mm 6mm 8mm	N=375 36 (9.6%) 224 (59.7%) 65 (17.3%) 50 (13.3%)	N=201 20 (10.0%) 114 (56.7%) 36 (17.9%) 31 (15.4%)	N=174 16 (9.2%) 110 (63.2%) 29 (16.7%) 19 (10.9%)	0.530
Injection area size, abdomen Stamp Credit card Playing card Post card	N=391 33 (8.4%) 108 (27.6%) 167 (42.7%) 83 (21.2%)	N=210 22 (10.5%) 48 (22.9%) 97 (46.2%) 43 (20.5%)	N=181 11 (6.1%) 60 (33.1%) 70 (38.7%) 40 (22.1%)	0.061
Needle reimbursement - Yes	142 (35.5%)	59 (27.8%)	83 (44.2%)	<0.001

Data are N (and percentage). Mean (SD), or median as noted

Predictors of lipohypertrophy prevalence

Based on stepwise logistic regression, five factors demonstrated a significant, independent correlation with LH prevalence (Table 4.5). Increasing BMI, needle reuse frequency, and lack of PN reimbursement had ORs for LH prevalence between 1.1 and 1.9 (all $p \leq 0.03$). Total weight-adjusted insulin dose and lack of correct site rotation had ORs of nearly 7.0 and 8.4, respectively, with p-values < 0.001. Nevertheless, confidence limits on these point estimates are rather wide, suggesting imprecision in the estimates.

Table 4.5. Stepwise Logistic regression results for prevalence of LH

Parameter	β	OR	95% CI of OR	p-value
Intercept	-4.249			<0.0001
Increasing BMI	0.0905	1.11	1.01, 1.19	0.0256

Frequency of needle reuse >7 Vs ≤ 7	0.5709	1.77	1.07, 2.92	0.0253
Lack of PN Reimbursement	0.6163	1.85	1.11, 3.10	0.019
Insulin Dose per Weight	1.9401	6.96	2.32, 20.8	<0.001
Correct Site rotation (No vs Yes)	2.1266	8.39	4.15, 17.0	<0.0001

For stepwise logistic regression, included variables are: Age (years), gender, BMI (kg/m^2), pen needle reimbursement status (Yes, No), Duration of insulin therapy (years), Instructions on injection (Yes, No), Site rotation (Yes, No), number of daily injections, Total daily insulin dose per weight (U/kg), HbA1c (%), needle length (≥6mm vs 4mm and 5mm), and PN reuse (Frequency ≤7, Frequency > 7). P value < 0.05 significant.

Relationship between PN reimbursement and study variables

The results that follow (Tables 4.6 – 4.9) describe the association between PN reimbursement and several domains of variables: demographic factors, clinical characteristics, PN utilization behavior, and diabetes- and insulin-related healthcare utilization and expenditures.

Table 4.6 includes comparisons of demographic characteristics by PN reimbursement status. Patients with PN reimbursement were older (62.4 vs 58.0 yrs., p<0.001) but there were no significant differences in gender or education. There was, however, a significant difference in distribution of medical insurance types between participants with and without PN reimbursement. The majority of patients with PN reimbursement had access through Urban Employee Medical Insurance (87.2%). The most common insurance type among those without access to PN was also Urban Employee Medical Insurance (41.1%), followed by Urban Resident Medical Insurance (26.1%) and New Rural Cooperation Medical Insurance (19.0%). Individuals with and without access to PN reimbursement also had variation in their income distributions. Patients without PN reimbursement likely had lower income, with 11.6% of patients reporting no income vs 2.1% in the reimbursed population.

Table 4.6.; Demographic Characteristics, by PN Reimbursement Status

Characteristics	Patients with PN Reimbursement (N=142)	Patients without PN Reimbursement (N=258)	p-value*
Patient age (years)			
Mean (SD)	62.4 (9.60)	58.0 (12.2)	>0.001
Median (Q1, Q3)	63 (57, 70)	59.5 (50, 67)	
Sex†			
Male (%)	65 (45.8)	135 (52.3)	0.252
Female (%)	77 (54.2)	123 (47.7)	
Education level†			
Primary school level or below (%)	19 (13.4)	30 (11.6)	
Junior school level (%)	51 (35.9)	75 (29.1)	
High school level (%)	31 (21.8)	68 (26.4)	0.220
Bachelor's degree (%)	38 (26.8)	80 (31.0)	
Master's degree or above (%)	1 (0.7)	5 (1.9)	
Other (%)	2 (1.4)	0 (0.0)	
Type of medical insurance†‡			
Urban employee medical insurance (%)	123 (87.2)	104 (41.1)	
Urban resident medical insurance (%)	12 (8.5)	66 (26.1)	
New rural cooperation medical insurance (%)	1 (0.7)	48 (19.0)	< 0.001
Commercial insurance (%)	0 (0.0)	2 (0.8)	
Free medical service (%)	2 (1.4)	24 (9.5)	
Other (%)	0 (0.0)	3 (1.2)	
More than 1 type (%)	3 (2.1)	6 (2.4)	
Income (monthly)r†			
No income (%)	3 (2.1)	30 (11.6)	
Below 1000 RMB (%)	4 (2.8)	16 (6.2)	
1001-3000 RMB (%)	92 (64.8)	109 (42.3)	
3001-5000 RMB (%)	35 (24.7)	71 (27.5)	<0.001
5001-10000 RMB (%)	6 (4.2)	25 (9.7)	
10001-25000 RMB (%)	1 (0.7)	4 (1.6)	
Above 25000 RMB (%)	1 (0.7)	3 (1.2)	

Q1 = lower 25^{th} percentile; Q3 = upper 25^{th} percentile; SD: standard deviation
*P-values were obtained using the χ^2 test, with the exception of education level where the Fisher Exact test was used; p-values < 0.05 were considered to be statistically significant
†Percentages represent column percentages
‡6 observations were missing responses for medical insurance

Table 4.7 compares the study population's clinical characteristics across PN reimbursement status. Type 2 diabetes was more common among participants with PN reimbursement (97.2% vs. 91.4%), whereas Type 1 diabetes was more common among those without reimbursement (8.6% vs. 2.8%) (p =.026). HbA1c, BMI, frequency of hypoglycemic events and duration of insulin treatment did not differ between participants with and without PN reimbursement (p>0.05). However LH was more prevalent among those who did not have coverage for PNs (59.3% vs. 41.6%, p = 0.0007); furthermore, the number of LH nodes was also higher in non-reimbursed group (2 vs. 1 per patient, p < 0.0001). Compared to those without insurance coverage for PNs, a higher percentage of patients with insurance coverage for PNs had cardiovascular disease (61.3% vs. 39.9%, p < 0.0001) and hyperlipidemia (54.2% vs. 18.6%, p < 0.0001) (see Table 4.5).

Table 4.7: Clinical Characteristics, by PN Reimbursement Status

Variable	Patients with PN Reimbursement (N=142)	Patients without PN Reimbursement (N=258)	p-value*
Type of diabetes†			
Type 1 (%)	4 (2.8)	22 (8.6)	0.026
Type 2 (%)	138 (97.2)	235 (91.4)	
Duration of time with diabetes (years)			
Mean (SD)	11.8 (7.26)	11.8 (7.74)	0.975
Median (Q1, Q3)	11 (7, 15)	11 (5, 16)	
HbA1c			
Mean (SD)	8.0 (1.53)	8.0 (1.76)	0.748
Median (Q1, Q3)	7.6 (6.8, 8.9)	7.6 (6.8, 8.8)	
Glucose control†			
HbA1c < 7% (%)	43 (30.3)	81 (31.4)	0.818
HbA1c ≥ 7% (%)	99 (69.7)	177 (68.6)	
BMI			
Mean (SD)	25.1 (3.09)	25.6 (3.20)	0.095
Median (Q1, Q3)	24.8 (22.7, 27.1)	25.4 (23.5, 27.6)	

Frequency of hypoglycemia in previous six months[†] 0 (%) 1-2 (%) 3+ (%)	 60 (42.3) 42 (29.6) 40 (28.2)	 104 (40.5) 66 (25.7) 87 (33.9)	 0.469
Duration of insulin therapy (years) Mean (SD) Median (Q1, Q3)	 5.9 (5.01) 5 (2, 8)	 5.4 (4.27) 4 (2, 8)	 0.444
Presence of CVD[†] (% Yes)	87 (61.3)	103 (39.9)	< 0.001
Presence of hyperlipidemia[†] (% Yes)	77 (54.2)	48 (18.6)	< 0.001
Presence of lipohypertrophy[†] (% Yes)	59 (41.6)	153 (59.3)	<0.001
Number of lipohypertrophy nodes Mean (SD) Median (Q1, Q3)	 1.5 (0.68) 1 (1, 2)	 2.7 (2.46) 2 (1, 3)	 < 0.001
Longest diameter of lipohypertrophy nodes Mean (SD) Median (Q1, Q3)	 16.8 (18.26) 10 (5, 22)	 16.1 (11.89) 15 (8, 20)	 0.122

*Differences in continuous variables were tested using Wilcoxon Rank Sum tests for non-normally distributed variables and the Student t-test for normally distributed variables; differences in categorical variables were tested using χ^2 tests; p-values < 0.05 were considered significant
[†]Percentages represent column percentages
CVD: cardiovascular disease; HbA1c = hemoglobin A1c; Q1 = lower 25th percentile; Q3 = upper 25th percentile; SD: standard deviation

PN training and injection practices are compared by reimbursement status in Table 4.8. The vast majority of patients reported receiving instructions on insulin injections and rotating injection sites regardless of reimbursement status. Patients without PN reimbursement did, however, report reusing PN significantly more (97.3% vs. 90.9%; p = .005) and reusing them more often than those with reimbursement (12 vs. 7 times; p < .001).

Table 4.8. PN Reuse and Related Factors, by PN Reimbursement Status

Parameter	Patients with PN Reimbursement (N=142)	Patients without PN Reimbursement (N=258)	p-value*
Subject ever received instruction on insulin injections† (% Yes)			
Yes (%)	131 (92.3)	229 (88.8)	0.265
No (%)	11 (7.7)	29 (11.2)	
Most recent receipt or review of injection instruction†			
Within the past 6 months (%)	14 (10.7)	18 (7.9)	0.952
Within the past 6-12 months	8 (6.1)	14 (6.1)	
More than 1 year ago	25 (19.1)	47 (20.5)	
More than 2 years ago	35 (26.7)	65 (28.4)	
More than 5 years ago	33 (25.2)	54 (23.6)	
More than 10 years ago	16 (12.2)	31 (13.5)	
Subject rotates inulin injection site† (% Yes)			
Yes (%)	105 (73.9)	212 (82.2)	0.052
No (%)	37 (26.1)	46 (17.8)	
Subject re-uses pen needles † (%Yes)	129 (90.9)	251 (97.3)	0.005
Number of times a single PN is reused by the subject			
Mean (SD)	12.9 (31.06)	19.5 (28.91)	< 0.001
Median (Q1, Q3)	7 (3, 15)	12 (6, 20)	

*Differences in continuous variables were tested using Wilcoxon Rank Sum tests for non-normally distributed variables and the Student t-test for normally distributed variables; differences in categorical variables were tested using χ^2 tests; p-values < 0.05 were considered significant
†Percentages represent column percentages
Q1 = lower 25th percentile; Q3 = upper 25th percentile; SD: standard deviation

Table 4.9 presents the results of comparisons of healthcare resource utilization and related expenditures by PN coverage status, which suggest minor differences. Number of diabetes-related outpatient visits were comparable between the two groups (1 vs. 2, p = 0.223). Even so, a larger percentage of those without PN coverage had at least 1 hospital stay (17.4% vs. 9.1%, p = 0.023 and greater daily total unstandardized daily insulin use (35.0 vs. 29.2 units, p = 0.026). After standardization (dividing daily insulin doses by the patient's body weight in kilograms (kg)), mean daily insulin dose remained significantly higher for those without PN reimbursement (0.50 vs. 0.45 units/kg body weight; p = 0.041). Comparisons of 6-month healthcare expenditures suggest that patients without PN reimbursement experienced greater hospital expenditures (1589 RMB vs. 773 RMB, p = 0.038), insulin costs (1591 RMB vs. 1328 RMB, p =0.003), and self-reported OOP costs (2217 RMB vs. 1226 RMB, p < 0.001). The total 6-month standardized expenditures, after excluding patients with missing cost data (1 observation had missing cost data for outpatient costs), were 6433 RMB for patients without PN reimbursement and 4432 RMB for those who had PN reimbursement (difference significant at p < 0.001). Diabetes related outpatient costs were not different between groups (p = 0.55).

Table 4.9. Estimated Diabetes and Insulin-related Healthcare Utilization and Expenditures, by PN Reimbursement Status

	Patients with PN Reimbursement (N=142)	Patients without PN Reimbursement (N=258)	p-value*
Resource Utilization in Prior 6 Months			
Number of Diabetes-related Outpatient Visits During Prior Six Months† Mean (SD) Median (Q1, Q3)	 2.65 (2.79) 1 (0, 6)	 2.50 (2.42) 2 (0, 5)	0.223
Any Diabetes-related Hospital Stay During Prior Six Months (% yes)†	13 (9.2)	45 (17.4)	0.023
Daily Insulin Dose (in Units) Mean (SD) Median (Q1, Q3)	 29.18 (13.72) 29.5 (18.0, 38.0)	 34.97 (20.28) 30.0 (20.0, 44.0)	0.026
Daily Insulin Dose per kg of Body Weight Mean (SD) Median (Q1, Q3)	 0.45 (0.21) 0.43 (0.28, 0.58)	 0.50 (0.28) 0.46 (0.28, 0.65)	0.041
Costs in Previous Six Months (reported in 2015 RMB)			
Diabetes-Related Outpatient Costs^ Mean (SD) Median (Q1, Q3)	 1105 (1160.5) 416 (0, 2497)	 1040 (1006.9) 832 (0, 2081)	0.558

Diabetes-Related Hospital Costs^ Mean (SD) Median (Q1, Q3)	 773 (2717.0) 0 (0, 0)	 1589 (4231.8) 0 (0, 0)	 0.039
Insulin Costs^ Mean (SD) Median (Q1, Q3)	 1328 (624.4) 1342 (819, 1729)	 1591 (922.9) 1365 (910, 2002)	 0.003
Reported OOP Costs Mean (SD) Median (Q1, Q3)	 1226 (933.3) 995.5 (679, 1580)	 2217 (2079.1) 1761.9 (891, 2937)	 < 0.001
Total Diabetes-Related Costs Mean (SD) Median (Q1, Q3)	 4432 (3376.3) 3850 (2135, 5388)	 6433 (5147.2) 5075 (3441, 7576)	 < 0.001

†Values represent outpatient visits and hospital stays during the past 6 months
*Differences in continuous variables were tested using Wilcoxon Rank Sum tests and categorical variables (any diabetes-related hospital stay) using χ^2 tests; p-values < 0.05 were considered significant
BMI = body mass index; DM = diabetes mellitus; kg: kilogram; OOP = out-of-pocket; PN = pen needle; Q1 = lower 25th percentile; Q3 = upper 25th percentile; SD = standard deviation;
^Unit costs: 1) insulin costs 0.25 RMB per unit; 2) outpatient/ER visits are 374.1 RMB per visit; 3) and hospital stays are 6,581 RMB per stay

Predictors of high healthcare expenditures

The results of a multivariable logistic analyses of factors related to having total direct healthcare expenditures above the 75th percentile are presented in Table 4.10. After adjusting for demographic and clinical characteristics, patients without PN reimbursement had 4.56 times the odds of having high costs as those with PN reimbursement (OR = 4.56, 95% CI = [2.14, 9.75], p = <0.001). Other factors in the model associated with having high costs included presence of retinopathy (OR = 2.08, 95% CI = [1.13, 3.85], p = 0.019), and presence of neuropathy (OR = 2.92, 95% CI = [1.56, 5.49], p < 0.001) and age (OR = 0.95, 95% CI = [0.92, 0.98], p < 0.001).

Table 4.10. Factors Associated with Total Direct Healthcare Expenditures in Previous Six Months in the Top 25th Percentile†

Parameter	OR	95% CI	p-value*
Age (year)	0.95	0.92, 0.98	<0.001
Sex			
Male	0.98	0.55, 1.75	0.938
Female (ref)	--	--	
Education Level			
High School and Below	0.77	0.37, 1.59	0.481
Bachelor's Degree and Above (ref)		--	
Type of Insurance			
Urban Employee Medical Insurance*	--	--	--
Urban Resident Medical Insurance	1.72	0.82, 3.63	0.854
New Rural Cooperation Medical Insurance	1.71	0.65, 4.49	0.888
Free medical service	1.00	0.32, 3.14	0.354
Other	2.23	0.31, 16.17	0.696
> 1 type	2.64	0.50, 14.03	0.492
Income			
No income (ref)	--	--	--
3000 RMB or below	1.30	0.44, 3.81	0.404
Above 3000 RMB	0.96	0.28, 3.33	0.693
Subject has some level of PN Reimbursement			
Yes (ref)	--	--	--
No	4.56	2.14, 9.75	<0.001
Type of Diabetes			
Type 1 (%) (ref)	--	--	--
Type 2 (%)	0.64	0.23, 1.85	0.413
Duration of diabetes	0.96	0.91, 1.01	0.131
Duration of insulin	1.03	0.95, 1.12	0.417
Hypoglycemia frequency in previous six months			
None (ref)	--	--	--
1 to 2	1.12	0.56, 2.25	0.558
3 or more	1.84	0.97, 3.48	0.062
BMI	1.09	1.00, 1.20	0.055
Presence of CVD	1.84	0.98, 3.48	0.060
Presence of hyperlipidemia	1.67	0.86, 3.24	0.130

Retinopathy	2.08	1.13, 3.85	0.019
Nephropathy	0.90	0.41, 2.00	0.798
Neuropathy	2.92	1.56, 5.49	<0.001
Other complication	1.03	0.35, 3.05	0.958

*p-values < 0.05 were considered significant
†Total costs under the 75th percentile of costs were considered to be low costs; costs at and above the 75th percentile were considered to be high costs; the cut-off point was based upon the distribution of costs in the data.
BMI: body mass index; CI = confidence interval; CVD = cardiovascular disease; OR = odds ratio; ref = reference group

SECTION 5: DISCUSSION AND CONCLUSION

Prior to this investigation, little was known about the problem of LH in China, in particular its relation to PN reimbursement. This research is the first to assess the prevalence of LH in China with clinical confirmation and accompanying insulin and injection technique data. The additional innovation in this research is the assessment of access to insulin delivery, as opposed to an evaluation of insulin effect and associated outcomes. This study established that the prevalence of LH in China (53.1%) is significant, that injection practices associated with LH in the literature (such as site rotation) are also risk factors in the Chinese patient population, the presence of LH is correlated with clinically meaningful differences in HbA1c, and patients who lack PN reimbursement exhibit higher frequency of PN reuse as well as higher insulin and total health care costs than those with reimbursement.

The population in this study was representative of the general diabetic population in China as reported by published surveys[34,37]. However, it is important to note that 87.2% of diabetics in this study were covered by the insurance scheme UEMI, which is not representative of the general Chinese population. This parameter may have been influenced by site selection, as tertiary settings are often more costly points of care and may draw patients with disproportional means. For this reason, extrapolation of findings beyond tertiary care settings should be done with caution.

The prevalence and risk factors findings of this study are similar to those generated by examinations of LH elsewhere. Studies conducted in Spain, Turkey, Italy and Norway, all utilizing trained nurses, also demonstrated the presence of LH in approximately half the study population (64.4%, 48.8%, 48.7%, 47.4% respectively)[48,52,64]. However, LH prevalence figures that rely on self-report are much lower, suggesting that professional examination is critical to diagnosis[64,55]. This also supports the ITQ guidance, which recommends annual injection site inspection, but also further highlights an opportunity for patient education on injection site inspection and LH detection.

The Spanish study of LH prevalence was the first to investigate the impact of LH lesions on differential insulin consumption. That research identified a consumption difference of 21 IU (48%) more insulin per day in those with LH than those without[48]. This study has identified a significant (11 IU) difference in insulin utilization between patients with and without LH (38.1 vs 27.1 IU, 40%, $p<.001$). The difference remained substantial after adjusting for BMI, which was not controlled in the previous research (.54 vs .41 IU/kg, 31.7%, $p<.001$). Since BMI was significantly higher for patients with LH in this study, a correlation with TDD was explored (Figure 4.1 – 4.3). The low R^2 values suggest that factors other than BMI affect insulin consumption.

A crossover euglycemic clamp study of Type 1 diabetes patients who received constant dose insulin injections into LH and normal tissue found that LH tissue significantly stunts insulin absorption. Post prandial blood glucose levels were also higher when insulin was injected into the LH tissue. Although the study was not powered for hypoglycemia, there was also a numerical difference in the prevalence between LH and normal tissue injections[46]. This has an important implication for the insulin-injecting diabetic population in China, namely that suboptimal insulin management is likely contributing to the observed rise in cost.

Diabetes is noted to be one of China's largest healthcare cost drivers[14]. Although little research has studied treatment-stratified diabetes patients in China, estimates of market sales of insulin in the country reached 9 billion dollars[73]. This research suggests that the adherence-adjusted cost of excess avoidable insulin use due to LH could be nearly 2 billion RMB, or onefifth of China's total insulin expenditure. The Blanco et al. study examined a similar relationship in Spain, estimating local opportunity cost of 122 million Euros in excess insulin consumption due to LH. That study did not, however, capture HbA1c values. No conclusion could therefore be drawn regarding the impact of excess insulin use and patient outcomes[48]. This particular limitation was addressed in the current research, which found that in addition to having significantly higher insulin utilization, patients with LH in China had higher HbA1c levels (0.5%). This further supports the hypothesis that injecting into LH lesions, which are believed to disrupt insulin absorption, leads to poor glycemic control at a substantial cost to the healthcare system. Efforts to increase insulin therapy adherence need to be accompanied by proper delivery education to avoid additional economic burden due to excess insulin consumption.

Pen needles are an important component of insulin delivery among insulin-requiring patients with diabetes. Despite this, only 35.6 percent of patients in this study reported having had any kind of reimbursement for their PNs (exact coverage could not be verified). This has important implications around patients' overall care, outcomes and costs. Patients who lack PN reimbursement may have significant unmet needs (compared to those who have their PNs reimbursed). These patients had a higher prevalence of LH and increased hospitalizations, insulin use, and overall costs. Although these associations do not indicate causality, they nonetheless indicate that these patients represent a population in which improvements in treatment are required to improve their outcomes and decrease overall costs.

Patients without PN reimbursement had greater costs than those with PN reimbursement, even after controlling for various clinical and demographic characteristics. A large portion of these increased costs is likely attributable to hospitalizations, as significant differences in hospitalization rates were observed in bivariate analyses and hospital costs are greater in scale than other costs (i.e., insulin costs). Although not directly attributable to PN reimbursement in this study, increased diabetes-related hospitalization and costs nonetheless indicate that these patients experience greater complications that require more intensive medical care.

Patients without PN reimbursement also had increased insulin costs, as a function of greater insulin utilization. The difference in daily average insulin costs (1.45 RMB per day) amounts to approximately 529 RMB per year. Despite their greater utilization of insulin, patients without PN reimbursement had similar average HbA1c levels as those with PN reimbursement, implying that these patients required more insulin to control their blood glucose. The clinical significance of this association is unclear. One reason why this was observed may be due to an increased observed prevalence of LH among these patients.

Despite most patients' in the study reporting they had received injection instruction at some point in their lives, only 16.8% received instruction in the year prior. Proper site rotation, as defined by this study to be both site rotation and moving the injection point at least 1 centimeter away from the prior injection point, was poor overall. However, upon sub-analysis, it was observed that while patients with PN reimbursement did not move the injection point at least 1 centimeter away from the prior injection point significantly more often, they did rotate sites significantly more often, which was associated with a lower prevalence of LH. The difference in site rotation practices among the reimbursed population may allude to a variance in the *type* of instruction received by those reimbursed for PNs, which was not assessed in this study. Patients who did rotate generally may have had the intention of proper site rotation, but lack of education on injection technique, or retention, could have undermined their efforts. This finding emphasizes the need for more frequent education on proper injection technique. Policies expanding healthcare worker compensation for patient education, and re-education, combined with training on techniques to improved health literacy among patients, may begin to address this issue.

In this study, needle reuse was also prevalent among all study participations (95%) and no correlation with LH was initially detected. Upon further investigation, it was determined that reuse frequency was associated with LH prevalence (p=0.003) suggesting that reuse is still a meaningful target for improvement. The Spanish LH study found that reuse greater than 5 times is significantly associated with the presence of LH in insulin-injection patients[48]. Another cross-sectional study by Ji et al., conducted in 2010 among 380 diabetes patients across 20 centers in mainland China, also found a significant positive relationship between the frequency of single needle reuse and LH[55]. In the Ji study, the mean number of uses per needle was 9.2, with approximately 26.8% of patients using the PN 10 or more times. Among patients who reused their needles, the most frequent reasons for reusing were for convenience and cost saving. In this study, more patients without PN reimbursement reused their PNs, and did so more frequently than those that had PN reimbursement. PNs are intended for single-use only, yet many patients—especially those without PN reimbursement—reused their PNs. It is possible that both repeated utilization of a single injection site, coupled with blunted needle tips (resultant of reuse), may be meaningful contributors of LH in insulin injecting patients[55].

With a growing prevalence of diabetes and use of insulin therapy the lack of reimbursement for PNs may have costly implications. Efforts to improve the quality of care for these patients should be multifaceted, incorporating increased and more frequent patient education, improvements in LH identification, management and monitoring, and implementation of measures to improve patients' use of prescribed treatment modalities such as PNs. This requires investment in both patient, caregiver and clinician education and promotion of existing guidelines.

Evidence suggests that patients' OOP costs may play a significant role in treatment adherence and clinical outcomes, leading to further potential medical and economic implications[74]. As saving money has been cited as a frequent reason for reusing needles, reimbursement of PNs may help to reduce the overall cost burden on the patient, thereby reducing needle reuse. This may in turn help to reduce LH associated with needle reuse. The healthcare system in China has historically adopted a principle of "broad coverage, with low basic level of benefits"—that is, providing coverage for the greatest number of people with the trade-off of limited levels of benefits. Despite the importance of PNs as a component of diabetes therapy, coverage of PNs has largely been overlooked. Though a larger emphasis is usually placed on drugs rather than medical devices, PNs represent a necessary component for all diabetic patients to reliably and safely inject their insulin. They could also have further implications for short term and cost containment and long-term patient outcomes.

Study Limitations

This study has several limitations. First, it is cross-sectional, in which both exposures and outcomes are measured at a single point in time. Therefore, although we can observe associations in patient characteristics and outcomes, we cannot evaluate temporal relationships or establish causality of these relationships. Further work should be performed to conduct longitudinal analyses of these outcomes to better understand these relationships over time. Longitudinal research would also allow us to better understand the etiology and potential for resolution of LH. Also, as this study was powered to assess prevalence of LH only, prospective randomized controlled trials are necessary to confirm the influence of injection technique training on correct site rotation, reduction in needle reuse and associated outcomes in patients with LH, to build on prior, uncontrolled work[52].

Patients' healthcare utilization (i.e., outpatient clinic visits and hospitalization) was solicited in the survey via self-report over a recall period of 6 months; this longer period of time may introduce recall bias, in which patients may have difficulty remembering their healthcare utilization during this period, thus resulting in potentially inaccurate estimates of outpatient clinic visits and/or hospitalization. This may be a concern more for minor types of healthcare utilization (e.g., outpatient clinic visits) rather than major events such as hospitalizations. In tradeoff, a shorter time period would increase the risk of not being representative of patients' healthcare resource utilization, especially in a chronic disease such as diabetes.

Total healthcare costs (as opposed to resource utilization) associated with inpatient stays, outpatient visits and insulin use were also not directly solicited from the patient. Therefore, published or private estimates of these costs from the literature or other sources of data were leveraged. Actual costs may vary widely, especially since different levels of resource intensity may be used depending on the reason for the outpatient visit or hospital stay. Subsequent research should be performed to measure actual healthcare utilization and costs for these patients, in order to shed further insight on the economic burden of these patients. Furthermore, future studies should look at such costs in the context of total medical expenditure for this population to be able to account for diabetes related comorbidities that are not captured in the definition of diabetes related expenditure.

Many factors can impact patients' quality of care and outcomes. Disease- and treatment-related factors such as comorbidities, severity of disease, local treatment practices, reimbursement policies for other diabetes-related treatments, and medication adherence can impact patients' outcomes. The study did not completely control for these factors, though it did control for certain patient comorbidities (such as cardiovascular disease and hyperlipidemia) and complications of diabetes (such as retinopathy, nephropathy, neuropathy, or other complications) as a proxy for severity of disease.

In order to make further recommendations on reimbursement policy, a thorough investigation of individual coverage policies is required. Coverage policies for PNs in China not only differ by insurance type but may also vary by geographic region. For instance, patients with diabetes enrolled in the UEMI in the Nanjing province pay between 5%-30% coinsurance (depending on age and setting of care) for PNs, whereas their counterparts in Beijing pay 100% of the costs for PNs OOP. Although this study did specify PN coverage, it did not solicit additional information on level of coverage. Assessment must also go well beyond PNs to understand the total diabetes management support that individual insurance plans offer to evaluate what combination of practices optimizes patient outcomes.

Finally, the studied patient population represents those from endocrinology clinics within four large tertiary hospitals in China, and thus may not be representative of the entire insulin-prescribed diabetes population in China. Larger studies across multiple, geographically-representative centers are needed to better understand the impact of PN reimbursement on health outcomes and costs nationally.

Even considering these limitations, this research provides empirical data regarding characteristics of China's insulin injecting population and healthcare cost burden for diabetic patients without PN reimbursement in China. This work addresses a binary question of whether having some extent of PN reimbursement helps alleviate the economic burden for patients who rely on PN-delivered insulin injections to manage their diabetes. Future research is needed to further evaluate how the degree of reimbursement (i.e., percent of costs reimbursed, type of procedures covered) may affect the healthcare costs for this patient population, especially those with low income.

Conclusions

In conclusion, this study demonstrated that LH is common in adult, insulin-injecting patients in China, at four major Tier 3 medical center clinics. It is associated with significantly worse glycemic control (HbA1c 0.5% greater) despite nearly one-third greater insulin consumption each day, compared to patients without LH. Major risk factors appear to be weight-adjusted daily insulin dose and lack of proper site rotation; other factors include BMI, frequency of needle reuse, and lack of pen needle reimbursement.

Insulin-dependent diabetes patients without PN reimbursement may confer a larger economic burden on China compared to those with PN reimbursement. To improve outcomes and decrease overall costs, interventions should be considered to improve the quality of care that these patients receive. Further research should focus on illustrating the reasons for hospitalization and increased insulin use among the non-reimbursed population. Investigation should also assess the impact of variations within and between polices to identify specific areas for improvement.

LH should be largely preventable by basic injection technique training to reinforce proper site rotation and reduction in needle reuse. Health care professionals should inspect patients' injection (and infusion) sites routinely, and provide education on proper injection technique. Additionally, providing increased coverage and reimbursement for PNs, along with patient education and increased awareness of coverage policies, may help to reduce PN reuse and potentially reduce LH and overall healthcare treatment costs for these patients[69,68].

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