Insulin treatment has been a life-saving and only medication for type 1 diabetes for almost a century. It was already explained that the burden of diabetes prevalence is largely due to the steep rise in the number of people with type 2 diabetes. For type 2 diabetes, most of the current guidelines recommend metformin as initial treatment. Metformin is a generic, relatively cheap and affordable diabetes medication. Since diabetes is a progressive condition, there is often a need to intensify the treatment after metformin.

According to the relevant guidelines, selection of medication to be added after metformin is based on several factors, including individual characteristics, presence of established atherosclerotic cardiovascular disease (ASCVD) or high ASCVD risk, other comorbidities, potential for weight gain, hypoglycemia, safety, tolerability, and the cost of medication [1].

Insulin remains the most effective diabetes medication and several improvements were made to the amino acid sequence of insulin molecule to enhance its properties, which resulted in the designer insulins or insulin analogues. Insulin analogues are characterized by faster onset and higher peak of action when administered subcutaneously compared to human insulin—bolus insulin analogues; or by prolonged duration of action, smoother and peakless profile—basal insulin analogues. First bolus insulin analogue was introduced in 1996, and first basal insulin analogue was introduced in 2000. Insulin analogues are usually offered at higher prices compared to human insulins and although they make the standard treatment for the majority of population with diabetes in developed countries, a lot of individuals in developing countries are still treated with human insulins.

The cost of insulin has been constantly rising in the past two decades [1, 2]. Unfortunately, in many countries insulin is not completely reimbursed and its high prices become a significant burden for the people with diabetes. This results in higher ‘out-of pocket’ expenditures, and contributes to a significant treatment non-adherence with devastating consequences [1, 2].

The cost of diabetes treatment, including insulin therapy, is a major factor in the cost-effective diabetes management. There is a huge discrepancy in the availability
of diabetes treatments between developed and developing countries. And even more
tragic is that this is also relevant for the insulin treatment.

According to the global survey conducted by the IDF in 2016, metformin and
sulfonylureas, as the most widely prescribed classes of oral antidiabetic treatment,
were always available in over 80% of high-income countries, compared with less
than 20% in low-income countries [3]. The situation with insulin in low-income
countries is even worse—inulin, in its various types, was always available when
and where needed in over 80% of high-income countries, compared with less than
15% in low-income countries [3].

The IDF survey has been an eye-opener for various stakeholders that many peo-
ple with diabetes in developing countries do not have uninterrupted access to basic
antidiabetic medication, including insulin as a life-saving medication [3].

A lot of people with diabetes, even in the most developed country of the world—
the US, are struggling with the affordability of insulin treatment. According to the
latest reports, 1 in 4 people with diabetes in the US is rationing the insulin supplies
[4]. The reason has been the rising cost of insulin, and such rationing could poten-
tially result in tragic consequences [4].

The example of insulin affordability makes the distinction between developed
and developing countries quite ambiguous. There are developing countries where
insulins are completely reimbursed for all people with diabetes requiring insulin
treatment, relevant for both human insulins and insulin analogues (e.g. the Republic
of North Macedonia), and developed countries where considerable share of people
with diabetes have to copay for insulin.

Initiatives are underway in several US states for limiting the insulin copayments
per certain amount monthly. The legislation would create a program allowing states
to procure insulin supplies at discounted prices and dispense them without prescrip-
tion renewals in selected cases.

That was certainly not the intention of the bright minds that discovered the insu-
lin back in 1921. Banting and Best vision was that everyone who needed insulin
would be able to afford it, which is why they sold the insulin patent to the University
of Toronto for just a dollar. Nearly 100 years later, many people with diabetes have
to pay significant amounts for their insulin medication [4].

In the past two decades, prices for the most commonly prescribed insulins have
increased by more than 700% in the US after adjusting for inflation [4]. It is not
quite transparent, which are the factors that have contributed to such increase in the
price of insulin treatment [4]. It has been reported in the US that people with diabe-
tes with annual income below USD 100,000 were more likely to ration insulin com-
pared to people with incomes above this level [4]. Such rationing was associated
with inadequate glycaemic control [4].

Innovation has often been cited as a reason for the rising insulin costs; however,
the price of the same insulins has increased several folds in the past 20 years. If a
long-term affordability of life-saving medication cannot be guaranteed in the US, it
would certainly be a challenge for a large part of the population with diabetes in
developing countries.
It is not only the medication - the other diabetes related costs exert an additional financial burden. People with diabetes in the US are experiencing more financial issues than those without diabetes, even when they have healthcare insurance [4]. Nearly 40% of people with diabetes reported financial challenges from medical costs, including medical debt or the inability to afford needed medical care [4]. This challenge was associated with high financial distress, food insecurity, treatment non-adherence, and missed or delayed medical care [4].

The importance of affordability of diabetes medication, and insulin treatment in particular, is emphasized in times of global crisis as during the latest pandemic with COVID-19. There is a risk of production and supply shortages of this critical medication, making the people with diabetes concerned about the availability of insulin treatment. Another factor is the increasing unemployment rate, affecting the healthcare insurance and financial resources of the people with diabetes, and their access to the life-saving medication.

People with diabetes in developed countries might experience difficulties with the access to diabetes treatment, including insulin treatment. Understandably, the situation is worse in the lower resource countries. Most of the novel treatments that have demonstrated benefits in people with established CVD, such as GLP-1RA and SGLT2i, are largely unavailable in developing countries due to their cost.

A huge problem with the access to medications is that price is usually similar in both developed and developing countries. In other words, global pharmaceutical companies are not adjusting their prices for the economic strength of the country. On the contrary, many of them challenged by the reference pricing system where prices in one country are used as a reference for prices in other countries are persistent in not adjusting the prices according to the local circumstances. In doing so, they try to prevent a domino-effect on prices across major geographical areas and markets. If faced with the possibility of reduction of prices, pharmaceutical companies are battling to keep them unchanged in the countries where they operate.

To put it in another perspective, pharmaceutical companies do not offer lower prices for medicines adjusted for the wealth of the country, thus making certain therapeutic options unaffordable for the majority of population with diabetes in developing countries. Pharmaceutical companies justify such high prices with the huge costs of research and development and the calculated health economics benefit for the healthcare system if the medication is used, taking into consideration both direct and indirect costs.

The problem is that those prices and health economic benefits are often calculated based upon the input variables as financially valued in the most developed countries, which are the largest markets for the companies. The products are then offered at the similar prices in both developed and developing countries, although the financial value of input variables would be much lower in developing countries. Direct and indirect costs in developing countries are lower; however, the input for justifying the prices is based on the costs from the most developed countries.

That is the reason why, very often, health economics analysis of cost-effectiveness of diabetes treatment cannot justify the price offered for the developing countries.
In many instances prices are much higher than the perceived healthcare benefits of the medication in developing countries. Hence, it would be difficult to demonstrate cost-effectiveness of the novel diabetes treatments in the setting of developing countries. Taking into consideration that the overall market for most diabetes medications is usually shared by only few global pharmaceutical companies, the developing countries have no other choice but to procure the medication for the prices offered.

There are two possibilities for developing countries in that situation. The first possibility is to allow wider use and reimbursement of high priced diabetes treatments exerting huge pressure on the healthcare budget. The second possibility is to limit their use, leaving major parts of population with diabetes without effective treatment.

The first possibility when countries with limited resources are committed to provide novel diabetes therapeutic options, exerts not only enormous pressure on the healthcare budgets, but is leaving other healthcare areas facing potential shortages. Those areas include the other NCDs that are becoming more prevalent in developing countries. Diabetes related costs have huge impact even on the normal functioning of the hospitals. In such scenario, developing countries are forced to continuously borrow money to cover this gap in the healthcare budgets, making them severely indebted and vulnerable, but doing their best to keep the system afloat.

Even when choosing modern insulin treatment, such as the first or second generation basal insulin analogues, cost-effectiveness of the treatment has to be considered. We have to consider not only the cost of a pen or a pack, but also the units of insulin required to achieve comparable glycemic control. It has been demonstrated that for achieving comparable glycemic control with the two first generation basal analogues, required doses are quite different. That may result in a different cost of treatment per person [5].

In the light of the latest COVID-19 global pandemic when whole countries and economies have been in lockdown with rising unemployment; countries have to borrow money to keep the societies living, and additional borrowing for providing the most modern treatment would be a challenge for the healthcare systems.

The second possibility would mean lack of access to modern diabetes treatments which increases the risk of poor glycemic control and diabetes complications. Recent medications, such as SGLT2i and GLP-1RA, have demonstrated benefits beyond glycemic control and lack of those medications additionally increases the cardiovascular risk in people with type 2 diabetes.

The role of some pharmaceutical companies is not limited only to the pricing of diabetes medications in developing countries. Developing countries usually have less stringent regulatory requirements for sales and marketing, as well as for medical and clinical activities of the pharmaceutical companies. Consequently, physicians tend to adhere less to diabetes care guidelines in developing compared to developed countries.

The regulation is either insufficient or completely absent, and there are numerous examples of physicians from developing countries being incentivized by certain pharmaceutical companies to increase the prescriptions of medications. In most
In extreme cases, the diabetes care guidelines could be largely influenced by pharmaceutical companies’ interests expressed through the scientific views of ‘independent experts’.

It is worth mentioning the situation of global pharmaceutical companies running clinical trials in developing countries. In many cases, study fees received by physicians in developing countries are relatively high compared to their wages, and could be a potential source of scientific bias when performing clinical trials.

Unfortunately, some of the pharmaceutical companies are not separating their sales and marketing from their clinical activities, making the clinical trials not the necessity to generate reliable clinical data, but a powerful tool to have principal investigators on their side when pursuing sales and marketing objectives.

Not only the national healthcare decisions are affected where the principal investigators could potentially have a huge influence through advisory, guidelines, or national procurement procedures, but the science and medicine could be affected, since it is difficult to be reassured that generated clinical data would be of acceptable integrity.

One solution would be to conduct studies in developing countries by independent clinical research organizations, and to completely disconnect clinical from sales and marketing activities of the companies. In addition, there have to be strict regulation in the developing countries on the means of financing of physicians by pharmaceutical companies.

Some of the pharmaceutical companies exert their influence on the healthcare systems in developing countries through certain patient organizations which they are covertly funding. Instead of pharmaceutical companies appearing in public and fighting for the high priced novel diabetes treatments, it is often few people with diabetes attempting to win the public support by requiring novel treatment for this vulnerable population. It puts additional pressure on the policy makers and influences their decisions which rely less on the evidence based on the cost-effectiveness of the medication, and more on the huge noise generated in the public space.

Digital and social media have recently played an important role in facilitating these processes driven towards additional pressure on the healthcare budgets, especially in the developing countries. Information is spread very fast through the social media, and it leaves little or no room for any cost-effective analysis of the treatment in question under the particular health economics circumstances of the developing country.

Innovations are something no one can live without, that is for sure. Innovations in medicines are welcome; they have significantly contributed towards better medical outcomes and increased life expectancy. However, in order to provide sustainable diabetes care, cost-effectiveness of novel treatments has to be taken into consideration under the circumstances of the developing countries.

Very often, due to the practices mentioned above, the penetration of more expensive diabetes medication has been higher in developing compared to developed countries. One example was the situation in the Republic of North Macedonia. In 2011, insulin analogues were contributing with 84% of the total insulin volume and 92% of the total insulin value in the country, after continuous growth in the previous
years (Fig. 4.1a, b) [6]. The penetration of the more expensive insulin analogues in the Republic of North Macedonia was higher compared to some of the most developed countries in the world, such as Germany or Norway (Fig. 4.2) [6].

The considerable increase in the penetration of insulin analogues, taking into consideration that insulins have been free of charge for the patients, was an unbearable cost for the Healthcare Insurance Fund and Government Programs. Unfortunately, the high percentage of individuals using insulin analogues was not paralleled with the improvement of glycemic control or prevention of diabetes complications [7].
On the contrary, people with diabetes were offered expensive insulin analogues free of charge with no or very limited possibility of glucose monitoring, since the test strips were quite expensive and were largely unavailable for the majority of people with diabetes. It was like driving the most expensive car in the world blindfolded. Such high penetration of insulin analogues was not mirrored by any monitoring of metabolic control parameters that are crucial for the prevention of diabetes complications.

To put the burden into broader context, if the cost for insulin analogues per person was analyzed in relation to the wealth of the country represented as GDP, and the index for Republic of North Macedonia was marked as 100, then the indices for the most developed countries in the world, such as Germany and Norway, would be 38 and 19 (Fig. 4.3a) [6]. Similar results were obtained if the cost of analogues was analyzed in relation to the GDP per person with diabetes (Fig. 4.3b) [6]. It means that the lower resource country, such as the Republic of North Macedonia, was paying three to five times more for modern diabetes treatment in relation to its wealth, in comparison with some of the most developed countries in Europe (Fig. 4.3) [6].

This situation is similar in other middle- or low-income countries, if we compare the healthcare resources allocated for modern treatment related to their wealth, to those of the developed countries.

It was already mentioned that 40% of all non-hospital medications reimbursed by the Healthcare Insurance Fund and Government Programs in Republic of North Macedonia, was spent on insulin and related supplies, such as insulin needles, glucagon, insulin pumps and ancillaries (Fig. 1.4). This cost did not include oral anti-diabetic medication, other form of diabetes medication, or direct and indirect costs of diabetes complications. It is a great example of how the cost of diabetes medication could bankrupt a whole healthcare system of a developing country. The
Fig. 4.3  Analogues value per person and as portion of GDP per person (index) (a), analogues value per person with diabetes and as portion of GDP per person with diabetes (index) (b), 2011 [6]

Fig. 4.4  Reduction of cost of insulin and related supplies in the Republic of North Macedonia, 2012–2016 [12]
pressure is higher in reverse relation to the wealth of the country—lower resource countries are affected the most.

To put it into perspective, the cost of insulin and related supplies for 4 years was equal to the cost of the huge, modern clinical complex that was planned to be built in the capital of the Republic of North Macedonia, and to serve the needs of the entire population across all clinical disciplines [6].

The Republic of North Macedonia has been characterized by high insulin penetration, as 43.8% of all diagnosed people with diabetes were treated with insulin in 2015 (Table 1.1) [7]. The relatively high insulin penetration could be explained by the limited access to non-insulin treatments, such as DPP-4i, SGLT2i and GLP-1RA. Therefore, people with type 2 diabetes requiring treatment intensification after metformin and sulfonylureas were more rapidly initiated on insulin treatment.

The country introduced several initiatives, as already described, including a strategic National Diabetes Plan, adopting international diabetes care guidelines under the local circumstances and publishing those as National Diabetes Care guidelines in the Official Journal of the country, formation of National Diabetes Committee, responsible for monitoring of adherence to diabetes guidelines by various stakeholders, and integration of diabetes care modules in the NeHS [8–11].

According to the guidelines, people with type 2 diabetes requiring insulin treatment were required to start on human insulins first, and then, under certain circumstances, they were allowed to be transferred to more costly insulin analogues. No limitations on the use of insulin analogues in people with type 1 diabetes were stipulated with the national guidelines.

In addition, central procurement of insulin and related supplies was introduced, together with parallel imports. Insulin in all its forms was provided 100% free of charge. On the other hand, the number of free test strips was increased seven-fold for the people with diabetes on insulin treatment. National Diabetes Committee identified numerous cases of people with type 2 diabetes treated with insulin analogues and having poor glycemic control. In many of those, cheaper human insulins were found to be better alternative to insulin analogues in terms of glycemic control. Penetration of insulin analogue was reduced from over 90% to 55% in 4 years, resulting in considerable savings.

Public procurement at central level could also drive the prices down, instead of each hospital or region procuring diabetes treatment supplies on its own. Bigger quantities usually result in reduction of prices due to the increased volume. Ensuring there is a competition among bidders drives the prices down, although the competition might be limited for certain diabetes medications.

Biosimilars and generics increase competition resulting in reduction of prices, after the patents of originator diabetes treatments expire. Encouraging generics and biosimilars producing pharmaceutical companies to compete at the centrally organized procurements could contribute to the cost-savings.

The centralized, integrated NeHS had a crucial role in the monitoring of adherence to the National Diabetes Care guidelines. The significant increase in glucose monitoring resulted in reduction of acute diabetes emergencies.
Such rationalization of treatment costs allowed for inclusion of novel classes of diabetes treatment, such as DPP-4i, SGLT2i and GLP-1RA, that were provided free of charge for selected people with type 2 diabetes according to the Guidelines.

By implementing all above measures, the biannual cost of the national, centralized, public procurement of insulin, insulin needles, test strips, glucagon, insulin pumps and related ancillaries was reduced from MKD 1.95 billion in 2012 to MKD 1.5 billion in 2014, and MKD 1.15 billion in 2016, despite the increase in the number of people with diabetes, increase in the cumulative annual growth rate of insulin volume by 5% over the period, increase in the number of free test strips by seven-fold, and introduction of novel diabetes treatment classes, such as GLP-1RA, SGLT2i, and DPP-4i (Fig. 4.4) [12].

This rationalization of costs confirms that even in the developing countries there could be enough resources if those are spent rationally and by practicing the evidence based medicine. The released resources could be used for additional initiatives to fight diabetes, for increasing glucose monitoring capacity, or for introduction of novel classes of diabetes treatment.

Those cost reductions resulted in reduced profits for some of the pharmaceutical companies, fiercely attacking the diabetes care policies and the people behind them. Hence, everyone involved in any such initiative for cost rationalization has to be prepared to be fiercely attacked. Attacks are usually orchestrated through selected few people with diabetes, using mass and social media.

Insulin treatment has to be provided to every person in need. If evidence based medical guidelines are practiced by every physician, in addition to initiatives resulting in reduction of prices of diabetes medication, it is possible to provide sustainable diabetes care in a setting with limited resources.

**What should be done to provide cost-effective diabetes treatment in developing countries?**

Each developing country should …

- … secure adherence to the National Diabetes Care guidelines, including the prescription of diabetes treatment;
- … consider central procurement of diabetes treatment while encouraging biosimilars, generics and parallel imports to reduce the prices;
- … use centralized, integrated NeHS to evaluate the cost-effectiveness of treatment;
- … allocate resources for sufficient glucose monitoring;
- … consider introduction of novel diabetes treatment for selected people with diabetes, according to the Guidelines.
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