WATER USE IN HUMAN CIVILIZATIONS: AN INTERDISCIPLINARY ANALYSIS OF A PERPETUAL SOCIAL-ECOLOGICAL CHALLENGE

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WATER USE IN HUMAN CIVILIZATIONS: AN INTERDISCIPLINARY ANALYSIS OF A PERPETUAL SOCIAL-ECOLOGICAL CHALLENGE

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HIGHLIGHTS
● Access to water shapes determines rise and collapse of civilizations
● Water conservation, human health and culture are closely connected
● Agricultural intensification triggers multiple cropping, irrigation and fertilization
● Mastering access to water will determine pace and sustainability of urbanization

GRAPHICAL ABSTRACT
ABSTRACT Settlement patterns and social structures have been shaped by access to water since the onset of human societies. This review covers historical and recent examples from Cambodia, Central Asia, India, Latin America and the Arabian Peninsula to analyze the role of water resources in determining the rise and collapse of civilizations. Over recent decades increasing globalization and concomitant possibilities to externalize water needs as virtual water have obscured global dependence on water resources via telecoupling, but rapid urbanization brings it now back to the political agenda. It is foremost in the urban arena of poorer countries where competing claims for water increasingly lead to scale-transcendent conflicts about ecosystem services. Solutions to the dilemma will require broad stakeholder-based agreements on water use taking into account the available data on water resources, their current and potential use efficiency, recycling of water after effective treatment, and social-ecological approaches of improved governance and conflict resolution.

KEYWORDS agroecology, historical water use, water footprint, water governance, urbanization

1 SETTING THE STAGE: WATER AVAILABILITY DETERMINED RISE AND FALL OF EARLY CIVILIZATIONS

It is currently understood that the East African Rift Valley had a pivotal role in the development of Homo sapiens who, possibly triggered by the encounter with new arrivals from southern Africa, started to migrate north-east, passing the Horn of Africa into Arabia and Asia some 60,000 years ago before eventually reaching Europe and the Americas[1]. Some 50,000 years later after the advent of the Neolithic Revolution, most of the first major settlements that are known start to surge in the semiarid drylands stretching from Asia to the Mediterranean. Neither the humid tropics, likely due to disease pressure, nor the temperate zones, given their harsh winters, seem to have favored early human agglomerations. Although founded likely 5000 years after Aleppo (Syria) and Jericho (Palestine[2]), one of the lesser known but well documented early structured urban settlements with 4-m-wide stone-built city walls and an estimated population of 5000 people was Jawa in Jordan[3]. Built in 3500–3000 BCE it is situated above the temporary water filled Wadi Rajil at the foothills of Jebel Druze (Jebel Arab), near a major trade route crossing semiarid Jordan from the southern Levant to Mesopotamia. Recent archeological research shows that its very existence is related to the advent of rainwater-irrigated terrace agriculture using small check dams, pools and canals[4,5]. Notably, the settlement itself is built 30–50 m above the wadi bottom as if the early city dwellers were more worried about the destructive power of water during the rare but powerful floods than about the painstaking work of getting it up from wells. It is unclear what made this great old city eventually collapse. As there is no evidence of major war-related destruction, it may well be subtle changes in the social-ecological system that has sustained it for centuries in the surrounding Jordanian basalt desert.

The first millennium BCE saw the invention, surge and subsequent spread of the increasingly elaborate Qanat or Karez irrigation system from ancient Persia throughout the Middle East[6] and Central Asia. It allowed the agricultural exploitation of vast lands in foothill and valley areas of the Himalayas, Hindukush and Karakoram, as well as the fringes of vast deserts in the Middle East stretching out as far as the Central Asian Tarim Basin. In this context, however, little is known about the historical interrelationships between irrigation practices and major urban settlements beyond rather mid-sized oasis systems such as Turpan, the important trade post along the Silk Route[7] and early Persian cities such as Gonabad, Khorasan-e Razavi Province, Iran.

In Asia, the pattern of spatial shifts in the settlements of the Great Indus Civilizations from 2500 to 1000 BCE was strongly influenced by the availability of, and access to, water, either due to reduced flow of rivers[8–10] around which these settlements had established or due to altered monsoon patterns[9]. The establishment and growth of the Harappan civilization (3300–1300 BCE) was initially favored by the continuous access to water from the once active Ghaggar-Hakra River system, claimed to be the Vedic Saraswathi. However, its eventual drying up, either due to a change in the river course induced by the tectonically active Himalayan plate[11–13] or climate change in North India[9] may have pushed the settlements eastwards. A recent analysis shows a process of urbanization (nucleation) and counterurbanization (denucleation) of settlements driven by push-pull factors of climatic conditions affecting access to water, both for settlements and for agriculture[9]. While urbanization occurred during periods of favorable monsoons, counterurbanization during the late Harappan time was apparently driven by the advent of weak summer monsoon rains[10].
Around 500 CE, Aflaj irrigation as a further intrinsic development of the Kareez system reached the eastern Arabian Peninsula where it triggered the transformation of temporary well-irrigated gardening (from 2500 BCE) into complex, year-round operating oasis systems. In Oman, this allowed the surge of oases, such as Itzki, that have existed since 600 BCE, and Nizwa (the capital from 600 to 700 CE) into major settlements. The far-reaching sociocultural implications of the new irrigation system were first described by Wilkinson [17] and its relatedness to agropastoral land use in different oasis types was confirmed a decade ago [19]. The continuous history of millennia-old foothill oases such as Jericho but also the much smaller ones of Itzki and Balad Seet [18] in Oman provides a vivid example of the crucial role of water resource reliability, rather than just the amount of available water, for settlement sustainability and continuity.

It is well known that the growth profile of the Mesoamerican Mayan civilization (< 2000 BCE to 1530 CE), one of the later cradles of civilization in the Americas, reflects the interacting effects of recurrent droughts upon rainfed agriculture on calcareous soils and of frequent wars between the city-states [17,18]. In this context the existence of irrigation-drainage-transportation canals to manage water at least since the late pre-Classical Period (c. 100 CE) is well understood. The elaborate canal water management systems allowed the survival of an estimated at least 10 people ha⁻¹ but as supported by recent LiDAR surveys may even have sustained much higher population densities across the El Petén and Yucatan Peninsula [19]. Infrastructurally similarly, and socially even more important, is the network of karst water reservoirs, the Cenotes, whose role has been strongly religiously codified [20].

Similarly, Chan Chan, capital of the pre-Inca Chimú Empire (900–1470 CE) was with an estimated 40–60,000 inhabitants the largest city of the pre-Columbian era in South America [21]. Its 500-year-old existence in the hyperarid N-Peruvian desert depended on a strictly hierarchically managed vast irrigation system distributing surface water runoff from the Andes to the coastal plains. A few centuries before (300–900 CE) the high thermal energy holding capacity of water running into channels that surrounded agricultural plots was used in the famous raised bed potato agriculture of Tiahuanaco at the shores of Lake Titicaca (north-western Bolivia). This system secured a large population of this high-altitude ceremonial center [22].

In southern and central Europe, the relationships between agriculture, urbanization, and cultural development can be typologized under two main strategies of food provisioning. First, ancient capitals often sustained themselves by the exploitation of vast hinterlands: in Rome (founded in the mid eighth century BCE, according to legend, and at its peak in the second century CE with an estimated 1 million inhabitants) this initially occurred by exploiting land resources in Italy, then by war-based imperial acquisitions of agriculture largely rainfed such as in Northern Africa or in Nile-fed Egypt. There the Shaduf-based basin irrigation system was the lifeline for millions of farmers and city dwellers for nearly 1500 years [23] that became connected to southern Europe. Exploiting the concept of virtual water, cheap, river-based long-distance trade was the main prerequisite of this water use strategy. This remained instrumental one millennium later for European trade hubs such as seventeenth century Amsterdam [24] and London [25].

The second European strategy to use scarce water resources effectively in the emerging larger settlements was to establish agricultural areas within the Medieval city walls to both provide fresh produce and properly deal with wastewater and night soil. Typical examples of this are the late sixteenth century Antwerp, with > 100,000 inhabitants the second-largest European city north of the Alps accounting at the time for 40% of the global trade, Brussels (50,000 inhabitants) and Lier (10,000 inhabitants) in Belgium (Fig. 1). Similar structures had Rothenburg ob der Tauber (Fig. 2) or Bamberg in southern Germany which as a World Heritage Site retains many city gardens until today [26]. Temperate climate-related low evaporative demands, water harvesting in cisterns and waste water recycling made northern European medieval cities likely much less dependent on immediate proximity to abundant river water than was the case under (sub-)tropical climatic conditions.

Given the paucity of reliable archeological records, little is known about the existence and agroecological challenges of early major settlements in Africa with the exception of Egypt and its elaborate irrigation agriculture. Early African agglomerations such as in Axum (Ethiopia) or Ounjougou (Mali) were small and emerged only by 200 BCE. In Asia, in contrast the areas of present-day China and the Indian subcontinent have a number of examples showing the rise and fall of ancient civilizations as determined by access to and mastering of water. In southern India, Thalakadu, a very active city in trade, culture and administration of the Hoysala dynasty during the thirteenth and fourteenth centuries, collapsed and finally became sand-encroached due to upstream mismanagement of the Kaveri River [27]. Although the damage to
the temples has been attributed to earthquakes\cite{30}, it was shown that damming the river in 1339 CE to divert water for feeding the city and agriculture, resulted in a peculiar and unexpected downstream movement of sand toward the city\cite{31} making it finally uninhabitable\cite{29}. Bhagar, once a flourishing trade city in Rajasthan, today stands as the remnants of an abandoned urban establishment that grew beyond the limits of its water source. This city was deserted quite quickly due to a severe drought that swept the entire area during 1783-86, a phenomenon known as the Chalisa Famine\cite{32}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Historical maps of the medieval Belgian cities Antwerp (1572, a), Brussels (1576, b), and Lier (1588, c) showing the inclusion of agricultural areas for food production and waste water/night soil deposition inside the mighty city walls. Source: Braun, G. and Hogenberg, F. Beschreibung und Contrafactur der vornembster Stüt der Welt. Cöln, 1574–1576; ©Sanderus-Antique maps.}
\end{figure}
Fig. 2  Rothenburg ob der Tauber, a medieval southern German town showing green spaces inside the city walls in a cadastral land register map of 1827 (a), and remaining agricultural land partly used for fruit tree and vegetable farming on an aerial image of 2019 (b). Map courtesy of Bayerisches Katasteramt München, Germany.

The sudden demise of the famous hydraulic city of Angkor, during 1431 is similarly attributed to a gradual weakening of its canal network infrastructure regulating the water supply to the city and its agriculture during a severe drought period following intense monsoon rains. The city was primarily built on and around a network of water canals to utilize the fluctuating water levels through the seasons. However, the decade-long severe drought prompted the dwellers to raise the exit levels for water flow. During the following intense monsoon rains the area was severely flooded, damaging the entire infrastructure. This eventually caused a decline in farm productivity and the collapse of the city to a level that made the entire empire crumble[33–36].
2 THE NEXUS: WATER CONSERVATION, HEALTH AND CULTURE

Diverse strategies were employed for storing and conserving water to mitigate its deficiency during odd seasons in water-stressed areas across the world. These reflect repertoires of locally relevant societal wisdom accumulated over millennia. For several thousands of years in the arid tracts of north-western India a range of traditional water storage systems such as stepped open wells (Jalara, Baoli), ponds (Bawari, Kund) and closed water bodies (Taankas) served as sources of domestic water supplies. The cultural restriction to modify these revered water storage systems may have prevented the buildup of the notorious Guinea worm (*Dracunculus medinensis*), also called the fiery serpent. Following the breakdown of such structural and cultural practices during British colonialism, this disease became widespread necessitating a national program of the Government of India to eradicate it. Further, morphological and functional similarity of these recent storage systems of north-western India with those of the stepped water storage and closed wells found in Dholovira, a Harappan city, suggest that such an underlying knowledge system and related cultural practices in dealing with water as the most critical resource determining human civilization may have evolved over thousands of years. This role is also evident from the establishment of the *Ery* system in dry tracts of southern India to harvest rain water. The system serially links ponds and minor lakes, mostly to meet agricultural water demands, thereby reflecting the evolution of traditional wisdom in water management. The sacrifice of animals (and apparently even humans, according to local ballads) to these tanks suggests a social commitment to build and judiciously use water from the *Ery* systems.

Across the world societies whose survival was directly linked to rainfed agriculture have developed and relied on astronomical observations that predicted the onset of favorable rains and have combined such knowledge accumulated over centuries into simple and locally relevant cultural practices. Farmers in Andean South America for instance are known to still use the visibility of certain stars to assess rainfall patterns. Similarly, the development of the highly precise Mesoamerican Mayan calendar is linked to the need to predict the onset of the rainy season. Farmers in Saurashtra, an arid province of north-western India, use the timing of blooming of specific trees, and the patterns of cloud formation during pre-rainy days as indicators of rainfall regularity. All of these are historical pointers to the struggles of human civilizations to gain knowledge about, and access to, water.

3 IRRIGATED AGRICULTURE: LINKING WATER RESOURCES TO SOCIOECONOMIC DEVELOPMENT

Over the last centuries largely triggered by growing population and changing consumption patterns the global demand for food and agricultural raw materials has been rising continuously. Worldwide rural societies with low population densities responded to growing demand mainly by cropland expansion. In contrast, intensification of land use by shortening fallow periods, multiple cropping and increased use of other inputs was key to fulfill growing demand when population densities were high. The latter also includes increased reliance on irrigation of agricultural land. This reliably enhanced productivity by reducing (1) drought stress of crops, (2) weed pressure in flood-irrigated crops such as rice or sugarcane, (3) crop heat stress by enhanced transpiration cooling, and (4) the diurnal temperature range in flooded rice fields. In many subtropical regions, exemplified by the North China Plain and the Indo-Pakistan Punjab, but also the Gezira scheme in Sudan, irrigation now allows crops to be grown throughout the dry period of the year and is therefore essential for direct land use intensification by multiple cropping systems. Over the last decade the technical availability of such options of land-use intensification has also led to major shifts in land ownership related to foreign investments, which particularly in Africa has been dubbed land grabbing.

The basic principles in the relationships between population density, aridity, cropland density, cropping intensity, and irrigation can well be visualized by segmenting and comparing global data sets. The mean per capita cropland area declines with increasing population density while the cropland density increases (Fig. 3(a)). Based on the maps from 2000, the per capita cropland use agrees very well with estimates based on case studies, the so-called Boserup land use sequence. Thereby, the proportion of the irrigated crop area is 20%, which is remarkably stable across different levels of aridity (Fig. 3(b)). Only when aridity is extreme with potential evapotranspiration being at least three times greater than annual
precipitation, the irrigated percentage of the crops becomes larger than 30% (Fig. 3(b)). The irrigated crop percentage is about 10% for population densities below 65 people km\(^{-2}\) but rises rapidly for pixels with higher population densities reaching almost 50% for regions with more than 1000 people km\(^{-2}\) (Fig. 3(c)). Remarkably, the increasing trend in the irrigated crop fraction is even more distinct for growing population density than for growing aridity. In general, the irrigated fraction is higher for rice than for non-rice upland crops but trends across aridity and population density classes are quite similar (Fig. 3(b,c)).

![Fig. 3](image_url)

**Fig. 3** Relationships between population density and per capita cropland use or cropland density (a), aridity and irrigated crop fraction (b), and population density and irrigated crop fraction (c) derived from global data sets with a resolution of 5 arc-minutes for year 2000. The fraction of the harvested crop area that is irrigated (b, c) was calculated as the sum of irrigated crop area divided by the sum of the total (irrigated and rainfed) crop area in the respective aridity or population density class.
In highly populated regions, per capita availability of land is low so that increased crop water supply is important to achieve high crop productivity needed to satisfy food demands. This is particularly the case in subtropical regions facing crop water shortages whose consequences may be mitigated by irrigation unless erratic droughts exhaust water resources. In contrast to fossil energy sources, water is largely a renewable resource circulating in the hydrological cycle. Water shortages are therefore less a result of limitations in the total volume of water available for human use, but instead frequently caused by the uneven distribution of water in space and time. To access water where and when it is needed, a gigantic network of more than 17 million artificial reservoirs with a total surface area larger than 50 Mha\(^2\) has been constructed and connected with agricultural fields by pipes and canals of distinct order. In almost all cases, storages such as reservoirs, lakes, rivers and aquifers providing water for irrigation serve more than one farmer, often thousands or even millions so that legal agreements, coordination, and management under elaborate governance systems are essential. It is estimated, that the network of canals and branch canals, distributaries and minors used to irrigate Pakistan’s Indus River Basin comprises 107,000 water courses with farm channels and field ditches totaling 1.6 million km to serve an irrigated command area of about 15 Mha\(^2\). In addition, in this basin shallow groundwater is pumped from more than a million wells. To install such infrastructure required a huge effort, but it may be even more challenging maintaining it in the longer term\(^{57,58}\). It is obvious that a failure in institutions responsible for organizing and coordinating water supply and drainage systems has serious short- and long-term consequences for the whole system comprising both farmer and consumer communities.

Over the past 60 years (1961–2017), the global total irrigated area doubled to more than 3.3 million km\(^2\)\(^{59}\). While only 21% of the total cultivated land is irrigated, it contributes to more than 40% of the global food production. Sub-Saharan Africa, with 3% irrigated agricultural land compared to the global average of 21%, indicates an important relationship between (largely lacking) irrigation-induced increases in agricultural productivity and undernourishment (25% in 2011–2013 compared to 12% globally\(^{59}\)). However, this also shows the major potential for production increases wherever the ecological, political, socioeconomic, and technological constraints to irrigation can be overcome.

While historically most food commodities have been produced close to the place where they were consumed, trade in a globalized world offers the opportunity to obtain virtual access to resources far away by importing food from elsewhere (Fig. 4). This strategy of importing virtual water is in particular useful when scarce local blue water resources requested by other sectors as well are substituted by green virtual water flows originating from regions with abundant precipitation. According to our calculations 22% of all virtual water flows are international, while the remaining 78% are domestic (between pixels within the same country). This demonstrates the strong link between urban areas consuming food products and rural agricultural areas producing the food\(^{62,63}\). This is why urban populations in semiarid West Africa\(^{64,65}\) and arid regions of the world with high per capita GDP, such as on the Arabian Peninsula\(^{66}\), can grow far beyond their local or domestic carrying capacity. While it is certainly an advantage to be less affected by anomalies in local weather and by harsh climatic conditions, long-distance connections also create new dependencies. Only a few countries worldwide, such as Argentina, Australia, Brazil, Canada, France, Kazakhstan, Thailand, the USA and New Zealand are net exporters of food products while the large majority of countries have implemented food import strategies to exceed local growth limits\(^{67}\). In all net food exporting countries irrigated agriculture contributes considerably to agricultural production, but the huge volumes of water needed are seen more and more critically, in particular during drought periods when water supply to other sectors is constrained. If the irrigation sector in one or more of these net exporting countries would experience serious constraints, such as by environmental regulations, trade barriers or severe droughts, global price shocks for food could be the consequence. Such shocks would obviously affect poor populations in low-income food-importing countries more than populations in wealthy states or the exporting countries. While the pattern and intensity of agricultural production is still far away from a state with globally optimized resource use\(^{68,69}\), trade has become an essential component determining food security in many countries.
Fig. 4  Aridity according to the CGIAR-CSI Global Aridity and ET database\textsuperscript{[60,61]} (a) and net virtual water flows (mm·yr\textsuperscript{-1}) calculated at 5 arc-minute resolution for North Africa, Europe and Central Asia considering 19 major food crops\textsuperscript{[62]} (b). These comprise wheat, maize, rice, barley, rye, millet, sorghum, soybeans, sunflower, potatoes, cassava, rapeseed, groundnut, pulses, citrus, dates, grapes, cocoa and coffee. Crops used as livestock fodder are also included in the calculations while pasture and extensive grassland is not. While grid specific production and water use was simulated, per capita crop consumption was assumed constant for all grids belonging to the same country\textsuperscript{[62]}. Blue indicates net virtual water outflow (water use for local crop production bigger than virtual water content of crops consumed) and red indicates net virtual water inflow (virtual water content in crops consumed greater than water use for crop production). Negative net virtual water flows in semi-arid, arid and hyperarid regions often indicate irrigated crop production while positive net virtual water flows show sinks (highly populated regions such as urban spaces and for regions in which crop production is not possible because of climatic constraints). At the global scale, 22\% of the virtual water fluxes are between and 78\% within nations.

4 Competing claims: agricultural versus urban water needs

Globally, the expansion of irrigated areas over the last century has led to a rapid increase in the annual irrigation water withdrawal from 590 to about 3000 km\textsuperscript{3}\textsuperscript{[70]} resulting in an ever aggravating competition for water resources. This conflict is becoming particularly obvious in the Middle East (Israel-Palestine-Jordan-Syria) and Central Asia (Mongolia-China), and in the several-decades-old international tensions among China, India and Pakistan, for the control of Asia’s biggest rivers originating in the Himalaya-Karakoram-Hindukush region.

Recent water crises in the Los Angeles area of California (USA) and in Cape Town (South Africa) are only the first alarm bells for increasing water conflicts between rural and urban needs. They illustrate that
humankind is running out of time to implement effective water saving policies and adaptation strategies thus creating awareness among the urban populace to reduce per capita water consumption.\textsuperscript{[74–75]}

Such conflicts are often overlooked in developing countries where trajectories of urban growth are often neither guided by a long-term plan nor do they address the supply potential of water resources. Bangalore (Karnataka, southern India) is a particularly pertinent example. Situated at 920 m on a granite plateau it is one of the very few cities in South-east Asian monsoon-driven, semi-arid climates that has no permanent rivers nearby. In 1537, when the city was established from a tiny thirteenth century village by the famous Hiriya Kempe Gowda I, a feudal king of the Vijayanagara Empire, drinking water requirements were met from lakes and artificial tanks established within the territories of the then small town.\textsuperscript{[76,77]} This continued for over a century as it grew under diverse rulers before it came under the reign of Wodeyars of Mysore during the seventeenth century and then under the administrative control of the Maharaja of Mysore during the end of the eighteenth century. Following this, water demand for the city was externalized to a huge reservoir built during 1933, about 35 km away from the city, exclusively to provide water to the city. However, unplanned developmental activities in its catchment area reduced the reservoir’s capacity and polluted its water to such a level that its original purpose is almost defunct. Inevitably, the externalization of water supply to the exponentially growing city was extended to the far-off Kaveri-Arkavathi river system. However, the pace of planning and execution to pump Kaveri water in different phases has not been able to keep up with the rapid growth. Importantly, filling in of tanks and lakes for construction, sedimentation, and blockage of natural drainage in and around the city area have contributed to the shrinking of lakes and overall declining surface water sources for agriculture that met urban needs for perishable goods. As a result of a typical red loop situation,\textsuperscript{[79]} for the past 50 years much of the drinking and irrigation water for agriculture, global flower production, and beautification of the city has been drawn from deep tube wells. Given political constraints, records from these wells are sketchy. However, recent data on well depth indicate a rapid fall of the water table in the Arkavathi Basin of Bengaluru to more than 400 m.\textsuperscript{[80]} This has led Bangalore authorities to discourage paddy rice production in Greater Bengaluru following thus the example of China where paddy cultivation is restricted to distance of 100 km from any major town. Currently, milking cattle, which are of high cultural value throughout India, can still be kept in large numbers in Bengaluru enhancing agricultural water use for cooling and unfiltered manure flushing into sewers which ultimately contributes to contamination of entire aquifers.\textsuperscript{[83]} In India, the water crisis is probably the most sensitive national political issue for the next decade, comparable only to the discourse with Pakistan about joint security.

5 CONCLUSIONS

Given the increasingly evident climate change effects, the numerous examples of access to and power over water determining the rise and fall of cities or entire civilizations throughout human history underline the need for more elaborate systems of water governance. Rapid rural-urban transformations leading to increasing shares of populations living in cities and relying on water for direct and indirect human needs will increase the pressure to regulate water utilization. While international food trade is one way to lessen the obvious agricultural dependence on access to water by externalization, it increases political dependence. Sustainable food trade therefore requires reliable international structures and agreements to avoid importers becoming captive to arbitrary political decisions made far away. In particular in and around cities, recycling and reuse of water will become an increasingly urgent task, but it requires strict enforcement of, and adherence to, laws that emphasize closed nutrient and waste cycles as well as use of effective technologies of water purification. With increasing densification and rising water use, particularly in poorer countries with temporary arid climates with so far low water consumption per capita, the nexus between availability of, and access to, high quality water and societal peace is likely to become the single most noticeable challenge for this century.

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Compliance with ethics guidelines

Andreas Buerkert, Kotiganahalli Narayanagowd Ganeshaiah, and Stefan Siebert declare that they have no conflicts of interest or financial conflicts to disclose. This article does not contain any studies with human or animal subjects performed by any of the authors.

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