Letters to the Editor

Tumor Incidence in Patients With Non-Alcoholic Fatty Liver Disease

by Dr. med. Yvonne Huber, Dr. med. Christian Labenz, Maurice Michel, PD Dr. med. Marcus-A. Wörns, Prof. Dr. med. Peter R. Galle, Prof. Dr. rer. med. Karel Kostev, and Prof. Dr. med. Jörn M. Schattenberg in issue 43/2020

Possible Mechanisms: Hyperinsulinemia and Endocrine Disrupting Chemicals

Nonalcoholic fatty liver disease is present in patients with obesity and type 2 diabetes mellitus (1). Concomitant hyperinsulinemia in such patients can promote tumor growth via the insulin receptor and activation of the mitogenic signaling pathways PI13-AKT-mTOR and RAS-MAPK. Furthermore, hypercholesterolemia which is often present in these patient groups can trigger tumor growth and development of metastases (2). Endocrine disrupting chemicals/EDCs (for instance, plastics such as bisphenol A, industrial solvents and lubricants such as polychlorinated biphenyles, pesticides, herbicides, and others) also can contribute to tumor induction. Many of these EDCs are lipophilic and remain stored in fatty tissue exerting mutagenic effects via epigenetic mechanisms such as DNA methylation changes (3). This way dichlorodiphenyltrichloroethane can cause breast cancer and testicular cancer and methyl bromide, a fungicide, as well as organochlorine and organophosphate pesticides can trigger prostate cancer. The main risk factor for skin cancer is ultraviolet radiation. However, besides nonalcoholic fatty liver disease and genetic predisposition EDCs are also a risk factor (4). After reviewing multiple epidemiological studies, the International Agency for Research on Cancer concluded that there is sufficient evidence to prevent many cancers (esophagus, gastric cardia, colon, rectum, liver, gallbladder, pancreas, breast, uterus, and others) by avoiding being overweight or obese. Acknowledging the current high prevalence of obesity of approx. 24 percent of adults and increasingly also amongst children and adolescents in Germany (with even higher prevalence rates in the United States of America), timely and good cancer prevention is recommended, as suggested by the authors (1). Moreover, patients should be examined for the possible presence of nonalcoholic fatty liver disease and existing hyperinsulinemia in such patients should be optimally treated. DOI: 10.3238/arztebl.m2021.0108

References

1. Huber Y, Labenz C, Michel M, et al.: Tumor incidence in patients with non-alcoholic fatty liver disease. Dtsch Arztebl Int 2020; 117: 719–24.
2. Gallagher EJ, LeRoith D: Hyperinsulinaemia in cancer. Nat Rev Cancer 2020; 20: 629–44.
3. Koch CA, Diamanti-Kandarakis E: Introduction to endocrine disrupting chemicals: is it time to act? Rev Endocr Metab Disord 2015; 16: 269–70.
4. Karimi K, Lindgren TH, Koch CA, Brodell RT: Obesity as a risk factor for malignant melanoma and non-melanoma skin cancer. Rev Endocr Metab Disord 2016; 17: 389–403.

Prof. Dr. med. Christian A. Koch, FACP, MACE
Assistant Prof. Dr. med. Michael J. Bartel
Prof. David S. Weinberg, MD, MSc
Department of Medicine, Fox Chase Cancer Center
Philadelphia, USA
christian.koch65@gmail.com

Conflict of interest statement
The authors declare that no conflict of interest exists.

In Reply:

We thank your correspondents for their interest in our work and for their interesting comments. In analyzing a large cohort from outpatient medical practices/primary care in Germany and observed that over a follow-up period of 10 years, patients with non-alcoholic fatty liver disease (NAFLD) have a higher risk of developing cancer (1) than people of comparable sex, age, and Charlson comorbidity index (CCI). We share our correspondents' concerns about the rising prevalence of overweight and obesity—especially in children and adolescents—as one of the underlying risk factors. In addition to further rises in fatty liver disease—which currently is certainly an underrecognized condition—type 2 diabetes and a further increase in tumor disease are to be anticipated. We believe that in addition to the academic discussion and the urgently needed scientific studies on NAFLD (3), enormous social and political efforts are required and preventive measures need to be strengthened. To this end, initiatives outside the healthcare sector with strengthened access to educational resources for younger people of all social strata are urgently required, as is information on foods. The effect of physical activity on physical and mental health and quality of life (4) is part and parcel. Ultimately, economic stimuli—in the shape of taxes or tax benefits—could be useful to support a health promoting lifestyle. In our opinion, such measures are the only way to affect positively the future challenges in the healthcare system that arise from metabolic disorders—including NAFLD. This, however, requires readiness of the society and the political will to support initiatives to promote metabolic health. DOI: 10.3238/arztebl.m2021.0109

References

1. Huber Y, Labenz C, Michel M, et al.: Tumor incidence in patients with non-alcoholic fatty liver disease. Dtsch Arztebl Int 2020; 117: 719–24.
2. Lazarus JV, Colombo M, Cortez-Pinto H, et al.: NAFLD—sounding the alarm on a silent epidemic. Nat Rev Gastroenterol Hepatol 2020; 17: 377–9.

3. Labenz C, Huber Y, Michel M, et al.: Impact of NAFLD on the incidence of cardiovascular diseases in a primary care population in Germany. Dig Dis Sci 2020; 65: 2112–9.
4. Huber Y, Pfirrmann D, Gebhardt I, et al.: Improvement of non-invasive markers of NAFLD from an individualised, web-based exercise program. Aliment Pharmacol Ther 2019; 50: 930–9.

On behalf of the authors
Prof. Dr. med. Jörn M. Schattenberg
PD Dr. med. Yvonne Huber
Schwerpunkt Metabolische Lebererkrankungen
I. Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz
joern.schattenberg@unimedizin-mainz.de

Prof. Dr. rer. med. Karel Kostev
Epidemiologie, IQVIA, Frankfurt

Conflict of interest statement
Prof. Schattenberg has received consultancy payments from BMS, Echosens, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Madrigal, Novartis, Pfizer, and Roche, as well as reimbursement of congress attendance fees and travel and accommodation costs from Gilead Sciences.

Prof. Kostev is employed by IQVIA.

Dr Huber declares that no conflict of interest exists.

CLINICAL SNAPSHOT

Stress Fracture of the Proximal Tibia in an 11-Year-Old Boy

An 11-year-old boy (a soccer hobbyist) presented to our department with a 1-month history of knee pain in the absence of any trauma event that he could recall. There were no B symptoms and no evidence of inflammation or nocturnal pain. The boy reported that playing soccer the previous day had caused exercise-related pain in the right knee to recur. The diagnostic work-up showed a clinically unremarkable, freely movable knee with no knee joint effusion or signs of internal damage. However, there was pain on palpation of the proximal tibia. Radiography revealed a fracture of the proximal tibial diaphysis that was in the process of healing, with early periosteal reaction and dorsal callus formation consistent with a stress fracture *(Figure a)*. After 4 weeks of avoidance of sport, rest, and analgesia, which represent the standard treatment—complemented if necessary by orthoses—the fracture was healed. A follow-up radiograph confirmed bone healing and showed marked callus formation and periosteal reaction (white arrows, *Figure b*). Stress fractures are rare in children/adolescents, but occur most frequently in the proximal diaphyseal/diametaphyseal tibia (sports involving sudden stops), followed by metatarsal fractures (endurance sports). From a pathophysiological perspective, repetitive trauma results in increased osteoclast activity that exceeds lamellar bone formation. The resulting resorption cavities ultimately lead to fractures. The fracture can initially only be visualized using magnetic resonance imaging, and on radiography only with a delay after healing.

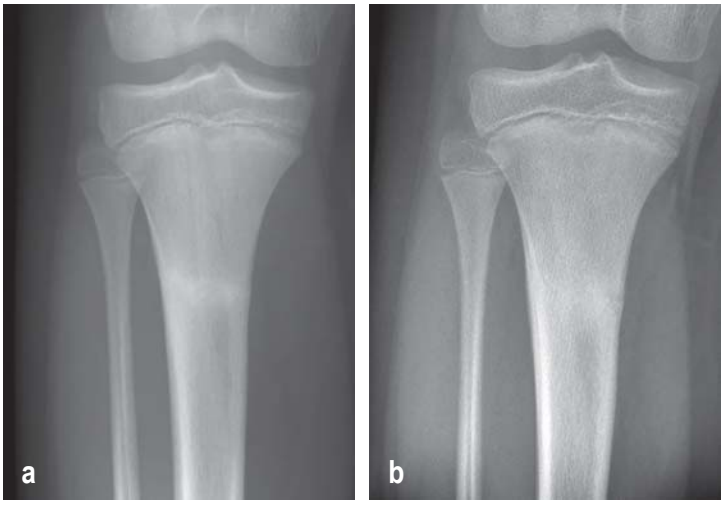

Figure: a) Radiographs 4 weeks after symptom onset; b) Follow-up radiograph at 6 weeks following diagnosis

Peter Heinz, Chirurgische Klinik, Universitäts-Kinderspital Zürich, peter.heinz@kispi.uzh.ch
Dr. med. Ileana Muster, Dr. med. Noémie Stähli, Interdisziplinäre Kinder-Notfallstation, Universitäts-Kinderspital Zürich

Conflict of interest statement: The authors declare that no conflict of interest existst.

Translated from the original German by Christine Rye.

Cite this as: Heinz P, Muster I, Stähli N: Stress fracture of the proximal tibia in an 11-year-old boy. Dtsch Arztebl Int 2021; 118: 272.
DOI: 10.3238/arztebl.m2021.0097