SUMMARY

The increasing life expectancy within the western population results in a higher number of people suffering from osteoporosis (characterised by a low bone mineral density - BMD) and sarcopenia (age-related decrease in muscle mass and quality). In addition to reduced muscle mass and thereby muscle force generating capacity, also the oxidative capacity of the muscle is reduced. These age-related changes in skeletal muscle may complicate the execution of daily activities as well as result in a higher fall risk. The low BMD in combination with fall incidents among older people results in a high fracture risk. Since fractures in older people are associated with a higher morbidity and mortality, it is important to prevent the loss of muscle performance (force generating capacity and oxidative capacity) and bone mass. Therefore, training should aim to increase muscle force generating capacity, oxidative capacity and bone mass. The aim of this thesis was to investigate 1) whether in older people, parameters of physical functioning are associated with bone quality and fracture risk and 2) whether it is possible to increase muscle performance (maximal muscle force and oxidative capacity) as well as bone mass by a combined peak power and endurance training in rats. This knowledge may help optimising training programs to improve and maintain musculo-skeletal health and may help identifying older people at high fracture risk for whom training intervention is strongly indicated.

To investigate how different measures of physical functioning are related to bone quality and fracture risk, we performed an epidemiological study in a large cohort of older Dutch men and women (Chapter 2). In Chapter 2 it is shown that in men, but not in women, higher physical performance scores were related to better bone quality cross-sectionally as well as longitudinally. In addition, in men high handgrip strength and physical performance scores are related to a reduced 6-year fracture risk. In women, low level of physical activity (< 120 min) was associated with a 40% higher fracture risk. Since the level of physical activity is not associated with bone quality, physical activity may be related to better balance, coordination or endurance of the muscles which may reduce the number of falls and eventually may contribute to a reduced fracture risk. All together, this suggests that these tests for physical functioning may be useful to identify older people at high fracture risk, but in a gender-specific
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manner. The causality as well as gender-specific differences in these relationships remain subject for further studies. It still remains to be determined what type of training is effective in reducing fall risk and whether this also results in a reduced fracture risk. Fracture risk may be reduced by increasing muscle performance and thereby reducing fall risk and/or by increasing bone quality. Testing physical functioning may provide an indication on the training-induced improvements and may be associated with reduced fracture risk.

The second aim of this thesis was to investigate whether combined peak power and endurance training enhanced muscle performance (muscle force generating capacity and oxidative capacity) and bone mass. Based on knowledge regarding the molecular regulation of hypertrophy and mitochondrial biosynthesis, it is expected that within a muscle fibre the increase in muscle fibre size and oxidative capacity is mutually exclusive. However, this interference between the adaptive response to peak power and endurance training may not account for the whole muscle, since different muscle fibres are recruited during distinct tasks and may adapt in a fibre type specific manner. During endurance training, the high oxidative muscle fibres are expected to increase their oxidative capacity, whereas in response to peak power training, low oxidative muscle fibres are expected to increase in size. To test whether by fibre type specific adaptation, the whole muscle can increase in size and oxidative capacity simultaneously, we investigated the effects of peak power training, endurance training and a combination thereof on the rat medial gastrocnemius muscle (GM) (Chapter 3 and 4). The rat GM is composed of a high and low oxidative compartment which are recruited according to specific tasks. During low intensity activities, the high oxidative compartment is active, whereas only during high intensity activities also the low oxidative compartment consisting of type IIX and IIB fibres is recruited. Such task specific recruitment in rat GM allows investigation of fibre type specific effects of concurrent training within one muscle.

To answer the second aim of this thesis, we performed a training study in rats. Rats were subjected to either peak power training (PT), endurance training (ET), combined peak power and endurance training (PET) or no-training (control). The training was performed on a treadmill 5 days/week for 6 weeks. The PET group performed two training sessions on training days (10 sessions per week) with an 8-hour rest between the training session.
In Chapter 3, the effects of peak power and combined peak power and endurance training on maximal force are presented. After peak power training alone, maximal force of GM was 10% higher compared to that of controls, which could not be shown after concurrent peak power and endurance training. In the low oxidative compartment, mRNA levels of myostatin and muscle ring finger 1 (MuRF-1) were higher after PT compared to those of controls and PET, respectively. Phospho-S6 ribosomal protein levels remained unchanged, suggesting that the elevated myostatin levels after PT did not inhibit mammalian target of rapamycin (mTOR) signalling. The different mRNA expression levels observed after PT and PET suggest that an interaction occurred between the training responses induced by peak power and endurance training. In conclusion, in compartmentalised rat GM, additional endurance training interfered with the adaptive response of peak power training and attenuated the increase in maximal force after peak power training. This suggests that even within a whole muscle, taking into account the fibre type specific adaptation, the increase in muscle force generating capacity is limited by additional endurance training.

In Chapter 4, the effects of different training modalities on oxidative capacity and regulatory factors of mitochondrial biosynthesis are presented. In the high oxidative compartment of GM, only endurance training and not concurrent peak power and endurance training induced an increase in succinate dehydrogenase (SDH) mRNA levels which may be the result of a reduction in receptor-interacting protein 140 (RIP140) mRNA levels. However, the increase in SDH mRNA expression levels did not result in increased SDH activity. For type IIB fibres of the low oxidative compartment of rat GM, peak power training induced a substantial decrease in SDH activity, which was not related to a reduction in the expression levels of SDH mRNA. Therefore, it is suggested that in compartmentalised rat GM, peak power on top of endurance training attenuates the mRNA transcription of mitochondrial proteins in the high oxidative muscle fibres and reduces mitochondrial activity in low oxidative muscle fibres.

In Chapter 5, effects of peak power training, endurance training and combined peak power and endurance training on the osteogenic response in rat tibia are presented. In bone, the adaptive responses of peak power training and endurance training were not expected to interfere with one another. The combination of peak power and endurance training may even enhance the osteogenic response. However, it is known that bone cells become desensitised to mechanical loading after only a few
loading cycles. By performing both types of training within one training session, the osteogenic response may be similar to that after one type of training only. Therefore, to restore mechano-sensitivity of bone cells, we induced a rest period between the two training modalities. With this rest period, the combination of peak power and endurance training could enhance the osteogenic response in rat tibia compared to either one type of training alone. Osteogenic response was measured as mRNA expression of mechano-sensitive genes involved in bone formation and regulation of bone turnover. Furthermore bone mass and turnover were determined at tissue level. Peak power training alone resulted in lower mRNA expression levels of osteoprotegerin (OPG) compared to those of ET, PET and controls. In addition, insulin-like growth factor 1Ea (IGF-1Ea), receptor activator of nuclear factor-κB ligand (RANKL) mRNA levels were lower after PT compared to those after ET. Additional endurance training on top of peak power training counteracted the reduction in mRNA expression levels of osteo-anabolic factors observed after peak power training only. Bone turnover measured by histomorphometry was not altered after training. Despite the fact that PET did not increase mean mRNA expression levels of genes involved in bone formation or bone formation as measured by histomorphometry, the variation of mRNA expression levels was substantially higher than that of the other groups. This elevated variation suggests that some rats responded to daily combined training for 6 weeks with a cumulative positive effect on mRNA levels of genes involved in bone formation. This suggests that combining peak power and endurance training with a rest period between the training sessions may prolong the transcriptional response of genes involved in bone turnover and may therefore in the long-term enhance the osteogenic response.

In conclusion, the epidemiologic study confirmed that parameters for physical functioning are associated with fracture risk. These measurements may help selecting individuals at high fracture risk for whom a training program is strongly indicated. However, combined peak power and endurance training as performed in our study is not appropriate to increase force generating capacity, oxidative capacity as well as bone mass. Despite this, the studies provided some indications for a training program design, being an optimal stimulus for the adaptive training response of muscle as well as bone. We suggest that when aiming to improve muscle force generating capacity
and oxidative capacity simultaneously, the endurance training should be performed approximately 2-3 times per week. To minimise protein and possibly mitochondrial degradation, hypoxia within fast muscle fibres should be prevented by performing the training at low intensities and/or with sufficient rest. To increase maximal muscle force, short bouts of peak power exercise should be performed with sufficient rest between the repetitions for recovery. In osteoporotic older people, training with a relatively high amount of low-impact exercises may be an appropriate way to increase bone formation, as high-impact loading increases the risk of (vertebral) fractures. We suggest that for bone, endurance training in addition to short periods of high-impact loading may be an effective strategy to enhance the osteogenic response. These training sessions for peak power and endurance should be separated by a rest period, as bone cells become desensitised to mechanical loading. Whether 8 hours is also optimal to restore mechano-sensitivity of human bone cells remains to be determined. Individual differences in training adaptation should be taken into account.